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

Amgen Protocol Number (AMG 562) 20170533

EudraCT Number 2017-005063-41

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Date:	10 January 2018
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Amendment 4 Date:	07 August 2019

Confidentiality Notice

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

Investigator's Agreement

I have read the attached protocol entitled "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 ", dated 07 August 2019, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

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

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

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

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1, 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

Study Phase: 1

Indication: Adult subjects with relapsed / refractory Diffuse Large B-cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL) or Follicular Lymphoma (FL)

Objectives:

Primary Objectives:

- Evaluate the safety and tolerability of AMG 562 in adult subjects with DLBCL, MCL or FL
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose (eg, recommended phase 2 dose [RP2D])

Secondary Objectives:

- Characterize the pharmacokinetics (PK) of AMG 562
- Evaluate anti-lymphoma activity of AMG 562

Exploratory Objectives:

[redacted]

- Evaluate the formation of anti-AMG 562 antibodies

Hypothesis:

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.

Endpoints:

Primary Endpoint:

- Safety: 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)s and clinical laboratory tests

Secondary Endpoints:

- 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 ($t_{1/2}$)
- Efficacy parameters:
  - ORR according to Lugano classification

- 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 Endpoints:

[redacted]

- Incidence of anti-AMG 562 antibody formation

Study Design:

This is a first-in-human (FIH), multicenter, non-randomized, open-label, phase 1 study which will consist of a sequential dose exploration part to evaluate safety and tolerability of AMG 562 in adult subjects with relapsed / refractory DLBCL, MCL, or FL. The dose exploration part will be followed by dose expansion to gain further safety and efficacy with AMG 562 in adult subjects with relapsed / refractory DLBCL. AMG 562 will be administered weekly as an IV infusion with or without a run-in phase (step-up dosing). The run-in phase consists of administration of a low dose on day 1 of treatment and a higher dose (target dose) on day 2. Additional dose steps may be administered subsequently at daily intervals. After administration of the target dose, treatment will continue with weekly administrations of the target dose.

Dose Exploration

The dose exploration cohorts will 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

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 shown Table 1 below. Once a

subject experiences a DLT, the dose for the subsequent cohorts will be recommended 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.

Table 1. Planned Dose Levels (IV)

Cohort	Dose (µg)	Cohort Size
1	0.1	1
2	0.3	1
[redacted]		

The DLRT may also recommend altering 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.

Dose Expansion

At completion of the dose exploration cohorts, additional subjects (up to 55) will be enrolled in a dose expansion cohort 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 covered by a protocol amendment to test 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 clinical activity of AMG 562 in the expansion cohort will be examined using a Bayesian predictive probability design. If 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 2.

Table 2. Futility Guidelines

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

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

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 17. The evaluations could occur more frequently if necessary to address emerging safety concerns

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% overall response rate, the expected 90% CI would be 29% to 52%.

Summary of Subject Eligibility Criteria:

Male or female subjects ≥ 18 year of age at the time of informed consent who have

- Relapsed / refractory DLBCL after appropriate prior treatment, with relapse after at least 2 lines of therapy, with one or more regimens including an anthracycline AND an approved anti-CD20 agent

or

- Relapsed / refractory FL after appropriate prior treatment, with relapse after at least 3 lines of therapy, with at least one or more regimens including an approved anti-CD20 agent

or

- Relapsed / refractory MCL after appropriate prior treatment, with relapse after at least 3 lines of therapy, with at least one or more regimens including an approved anti-CD20 agent

at time of screening. The diagnosis must be biopsy proven and subjects must have measurable disease at screening as defined in the inclusion criteria. Subjects who received prior CD19 directed CAR-T cell therapy are excluded.

Investigational Product

Amgen Investigational Product Dosage and Administration:

AMG 562 will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

AMG 562 is supplied as a sterile, preservative-free lyophilized powder for IV administration after reconstitution with sterile water for injection (WFI).

AMG 562 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 562.

The initial duration of infusion will be [redacted] This duration may be extended up to 6 hours for future dose cohorts or subsequent cycles for all subjects in the initial dose cohort based on review of safety and PK data by the DLRT.

- Minimum hospitalization times for subjects will be as follows:
- **Without step-up dosing:**
    - 72 hours after infusion at C1D1 and C1D8
    - 48 hours after infusion at C1D15 and C1D22 if there are no adverse events ≥ grade 1 up to day 15, otherwise 72 hours.
    - For all subsequent infusions subjects should be monitored in hospital or outpatient clinic for at least 4 hours after start of each infusion with hospitalization at the discretion of the investigator

- **With step-up dosing:**
  - 72 hours after infusion at day 1, after every step dose infusion and for the first two infusions at target dose (similar to C1D1 and C1D8 without step-dosing)
  - 48 hours after the 3rd and 4th infusion at target dose if there are no adverse events ≥ grade 1, otherwise 72 hours.
  - For all subsequent infusions, subjects should be monitored in hospital or outpatient clinic for at least 4 hours after start of each infusion with hospitalization at the discretion of the investigator

The DLRT may recommend on changes in hospitalization requirements after review of available safety data.

Treatment can be administered as long as the subject is deriving benefit per the judgment of the investigator, unless one of the criteria for permanent discontinuation of treatment is met. Treatment can be discontinued 4 weeks after a CR/CMR is confirmed by the investigator after consultation with the Amgen Medical Monitor.

Procedures: After providing informed consent, eligible subjects will undergo the following assessments during this study: physical examination, neurological examination, Eastern Cooperative Oncology Group (ECOG) status, height, weight, vital signs, pulse oximetry, ECG triplicate measurement, laboratory assessments (including serum pregnancy test, if applicable, coagulation, hematology, blood chemistry profiles, urinalysis, hepatitis serology, and anti-AMG 562 antibody test), biomarker and PK assessments, immunoglobulin levels (IgG, IgA, IgM), PET-CT (per standard of care), and bone marrow biopsy (per standard of care). Reporting of adverse events, disease related events, and cases of pregnancy and lactation will be performed as described in the study procedures.

Statistical Considerations: The primary analysis for the dose exploration part will occur when targeted enrollment is complete and each subject either completes 3 months on study or is taken off from the study by the Investigator. The primary analysis for the dose expansion part will occur when targeted enrollment is complete and each subject had the opportunity to receive at least 3 months of treatment at the target dose.

In the dose exploration part, the DLRT will review the safety data after each cohort and make a recommendation on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. In the dose expansion part, efficacy futility and safety will be assessed using a Bayesian predictive probability design.

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic, efficacy and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. ORR will be presented with 90% exact CI. PFS will be summarized using the Kaplan-Meier method. Graphical summaries of the data may also be presented.

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

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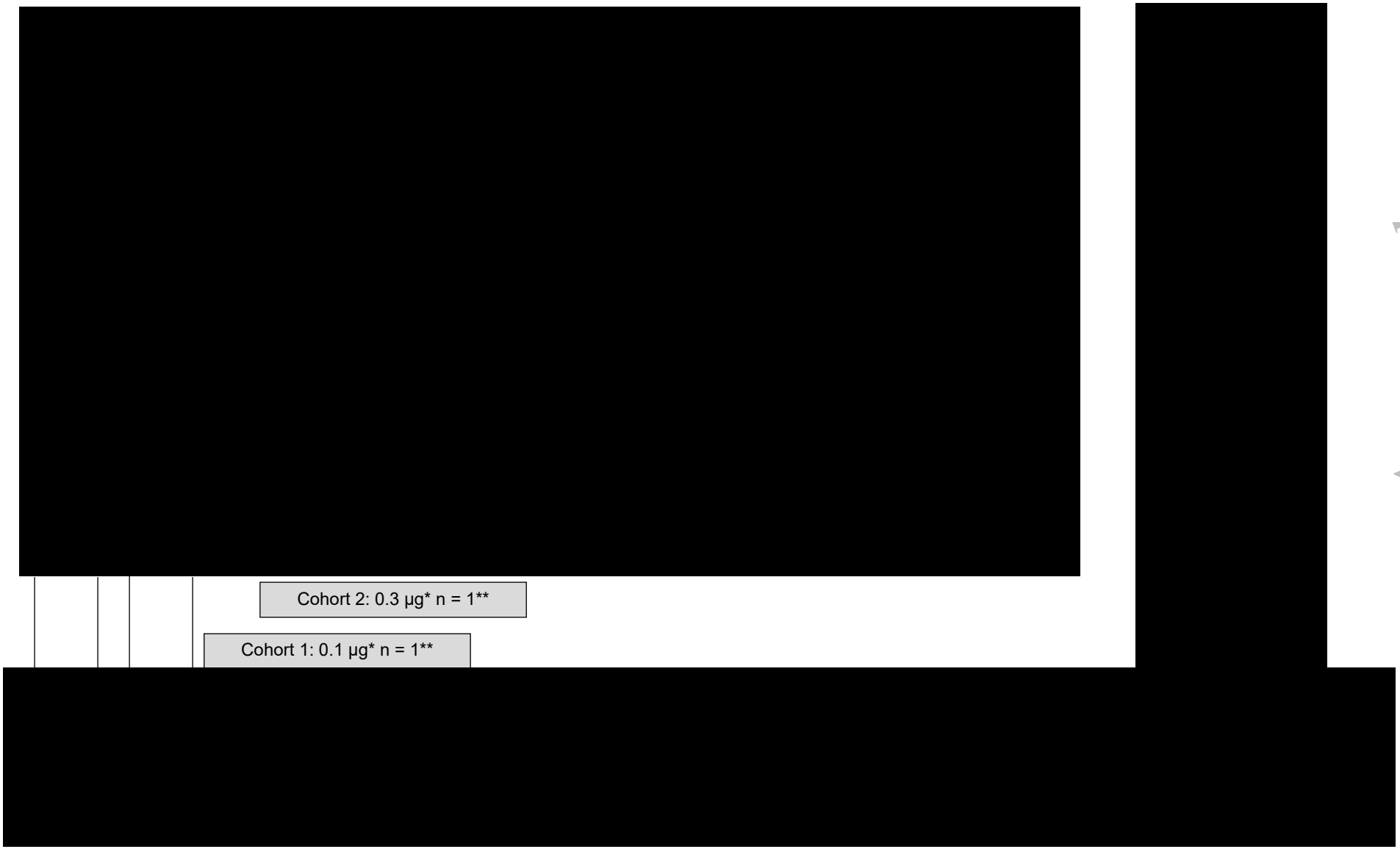
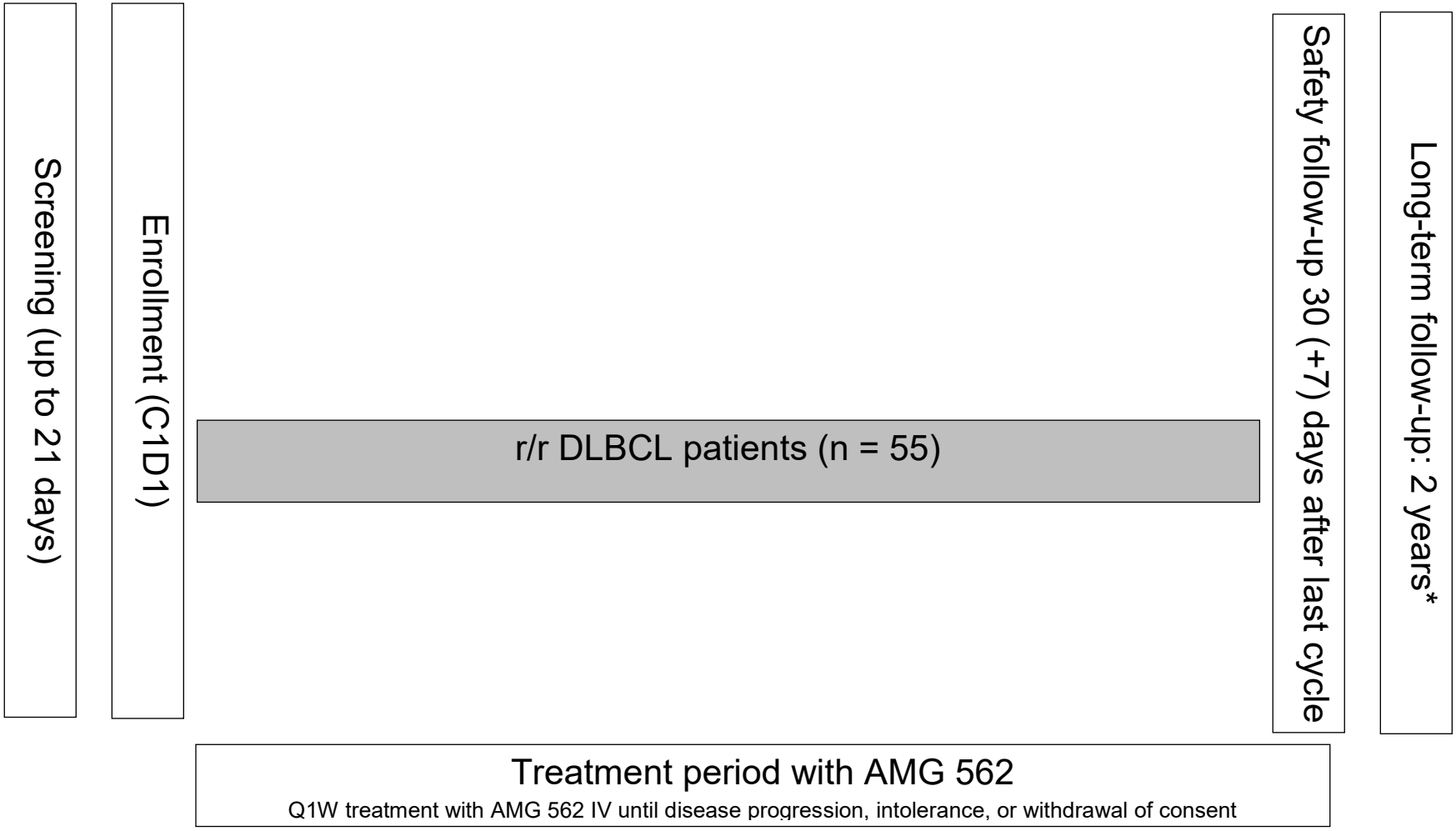
SCHEMA: Part 1 - Dose Exploration (n ~ 30)



SCHEMA: Part 2 - Dose Expansion



* From first dose of AMG 562

Study Glossary

Abbreviation or Term	Definition/Explanation
^{18}FDG-PET	18-fluorodeoxyglucose-positron emission tomography
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLRM	Bayesian logistic regression model
BM	bone marrow
B-NHL	B-cell Non-Hodgkin Lymphoma
CAR	chimeric antigen-receptor
CBC	complete blood count
C_{max}	maximum concentration
C_{min}	minimum concentration
CMR	complete metabolic response
CNS	central nervous system
COO	cell-of-origin
CR	complete response
CRF	case report form
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebro spinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DILI	drug induced liver injury
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
EC_{50}	half maximal effective concentration
EC_{90}	effective concentration leading to 90% response
EDC	electronic data capture
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation or Term	Definition/Explanation
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 (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)	the time when the last subject is assessed or receives an intervention for evaluation in the study.
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
FISH	fluorescent in situ hybridization
FSH	follicle stimulating hormone
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor
HepBsAg	hepatitis B surface antigen
HepCAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplant
IB	Investigator's brochure
IC	investigator's choice
ICF	Informed consent form
ICH	International Conference on Harmonisation
IgA	immunoglobin A
IgG	immunoglobin G
IgM	immunoglobin M
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IRR	infusion related reaction
IV	intravenous
KM	Kaplan-Meier
MABEL	minimum anticipated biological effect level
MRD	minimal residual disease

Abbreviation or Term	Definition/Explanation
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHL	non-Hodgkin's lymphoma
ORR	objective response rate
OS	overall survival
PB	peripheral blood
PD	progressive disease
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
Q-PCR	Quantitative Polymerase Chain Reaction
QTc interval	QT interval corrected for heart rate using accepted methodology
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
[redacted]	
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 products are administered to the subject
TBL	total bilirubin
T_{max}	time of maximum concentration
TPI	toxicity probability interval
ULN	upper limit of normal
WBC	white blood cell
WHODRUG	World Health Organization Drug

TABLE OF CONTENTS

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

- Evaluate the safety and tolerability of AMG 562 in adult subjects with DLBCL, MCL or FL
- Estimate the maximum tolerated dose (MTD) and/or a biologically active dose (eg, recommended phase 2 dose [RP2D])

1.2 Secondary

- Characterize the pharmacokinetics (PK) of AMG 562
- Evaluate anti-lymphoma activity of AMG 562

1.3 Exploratory

- Evaluate the formation of anti-AMG 562 antibodies

2. BACKGROUND AND RATIONALE

2.1 Disease

The annual incidence of Non-Hodgkin's Lymphoma (NHL) in Europe and the United States is estimated to be 15 to 20 cases/100.000 (Fisher and Fisher, 2004). NHL is a heterogeneous set of malignancies with many histologic subtypes. For practical clinical purposes, NHL can be divided into indolent and aggressive lymphomas. Most NHLs are B-cell derived (90%) and express common B-cell antigens such as CD19, CD20, and CD22 (Katz and Herishanu, 2014; Evens and Blum, editors, 2015).

DLBCL is an aggressive Lymphoma and the most common subtype of NHL, accounting for 30% to 40% of cases. The incidence is approximately 8 cases per 100 000 and rises with age; the median age at diagnosis is 70 years (Haematological Malignancy Research Network). Distinct patterns of gene expression are observed within DLBCL, with different prognostic and potentially predictive implications. The main histological subtype of indolent NHL is FL, which accounts for approximately 20% of all NHL. MCL comprises 9% of all NHL. Management of NHL varies considerably, ranging from no initial therapy at all to multimodality therapy using radiotherapy, cytotoxic chemotherapy, and or chemoimmunotherapy (Evens and Blum, editors, 2015).

Left untreated, DLBCL is uniformly fatal. Anthracycline-based frontline chemotherapy, introduced in the 1970s, resulted in the long term cure of 30% of patients (DeVita et al, 1975). Twenty-five years later, introduction of the human-mouse chimeric monoclonal anti-CD20 immunoglobulin G (IgG) rituximab increased the cure rate significantly and is now a standard agent in frontline therapy, resulting in cure for 60% of patients (Sehn and Gascoyne 2015).

Patients with DLBCL who do not respond to frontline therapy, or who experience relapse after a remission, are generally considered incurable unless able to receive either high dose chemotherapy (HDT) with autologous or allogeneic haematopoietic stem cell transplant (HSCT) (Robinson et al, 2016). HSCT is preceded by a course of salvage chemotherapy. "Chemoresponsivess", indicating a partial response (PR) or complete response (CR) to salvage chemotherapy, has been used as one criterion to define HSCT eligibility, since early trials demonstrated the extremely poor outcomes of patients without an objective response to salvage chemotherapy (Philip et al, 1987). Despite the improvements observed since the introduction of rituximab into front-line treatments, relapse continues to be observed in 10 to 20% and 30 to 50% of patients in favorable and poor prognostic groups respectively (Martelli et al, 2013). The efficacy of salvage regimens have been compared in 2 large, multicenter randomized trials, CORAL (R-DHAP vs R-ICE) and NCIC Ly.12 (R-DHAP vs R-GDP) (Crump et al, 2014; Gisselbrecht et al, 2010). A third trial, ORCHARRD, tested an alternative anti-CD20 agent, ofatumomab, versus rituximab in combination with DHAP (Van Imhoff et al, 2014). The different response and survival rates observed in these large trials may be attributed to heterogeneity in patient selection criteria as well as in the nature and timing of post-treatment assessments. Nonetheless, these results 1) fail to demonstrate superiority of any specific regimen and 2) underscore the need for new agents in the salvage treatment of this disease. Recently axicabtagene ciloleucel, YESCARTA, and tisagenlecleucel, KYMRIAH, were approved in the US based on single arm study for refractory or relapsed large B-cell lymphoma after two or more lines of therapy. Although response rates compare favorably with other therapies in this setting, serious side effects are frequent and clinical experience stems mostly from patients with good performance status (YESCARTA prescribing information, 2017; KYMRIAH prescribing information, 2018).

Thus, there is a significant medical need for novel, effective and well tolerated therapies in relapsed or refractory DLBCL.

Newly diagnosed FL and MCL is generally treated with chemoimmunotherapy. Earlier stages of FL can be managed by watch and wait or radiotherapy in cases of localized disease. The majority of MCL patients present with advanced disease and require treatment at diagnosis. For MCL, eligible patients generally receive consolidation through autologous transplantation, which confers prolonged progression free survival. For FL and older MCL patients Rituximab maintenance should be offered after standard chemoimmunotherapy (Evens and Blum, editors, 2015).

There are several treatment options for symptomatic relapsed or refractory FL patients, including chemoimmunotherapy, immunotherapy, chemotherapy, radioimmunotherapy, antibody drug conjugates and novel targeted therapies. In general, response rates and response durations decrease substantially with each line of treatment and cumulative toxicities of multiple treatment lines can reduce quality of life. Relapsed or refractory FL is considered incurable with few exceptions (Evens and Blum, editors, 2015).

For treatment of relapsed or refractory MCL ibrutinib is a preferred agent but other targeted agents, chemoimmunotherapy and autologous as well as allogeneic stem cell transplantation are used in this setting. As with FL, therapies become less effective with successive lines of treatment and advanced MCL cannot be cured with standard therapies (Evens and Blum, editors, 2015).

In conclusion there is a significant medical need in the relapsed or refractory setting in MCL as well as in FL for novel treatment options with higher response rates and increased duration of response to reduce burden caused by multiple lines of therapy and to provide effective treatment options for patients with aggressive disease.

2.2 Amgen Investigational Product Background

BiTE® antibody constructs (bispecific T cell engagers) have been designed to direct T cells towards target cells. AMG 562 consists of 2 single chain variable fragment (scFv) binding domains, specific for CD19, an antigen expressed by B cells, and the epsilon subunit of the CD3 complex present on T cells. The cross-linking of the CD19 and CD3 antigens mediated by the BiTE® triggers target cell specific cytotoxicity closely resembling standard cytotoxic T lymphocyte activation.

AMG 562 is a BiTE® antibody construct belonging to the so called Half Life Extended (HLE) BiTE® antibody constructs, which is being developed with the intent to treat patients with DLBCL, MCL, and FL. Compared to canonical BiTE® Antibody constructs like blinatumomab, a scFc fragment has been introduced into the molecule in order to

prolong its half-life. T cells are bound by its anti-CD3 moiety, whereas lymphoma cells are bound by the anti-CD19 moiety. This feature of AMG 562 allows it to transiently cross-link malignant cells with T cells via their CD3 complex, thereby inducing T-cell mediated killing of the bound malignant cell. In preclinical models, AMG 562-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent lysis of malignant cells by AMG 562-activated T cells closely resembles a natural cytotoxic T-cell reaction.

Refer to the specific section of the Investigator's Brochure (IB) for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s) of AMG 562.

2.2.1 Pharmacology

The activity of AMG 562 requires the simultaneous binding to both target cells and T cells. The pharmacological effect of AMG 562 is mediated by specific redirection of previously primed cytotoxic $CD8^+$ or $CD4^+$ T lymphocytes to kill $CD19^+$ cells. AMG 562 is a potent molecule showing mean half-maximal lysis of human tumor cell lines by human effector cells in vitro over a range of 0.031 to 1.870 pM. In addition, AMG 562 induced a dose-dependent lysis of primary human B cells by autologous T cells with EC_{50} values for the individual dose-response curves varying between 0.060 and 1.422 pM.

As part of the T cell activation process, BiTE® antibody constructs, such as AMG 562, cause the formation of a cytolytic synapse between T cells and target cells. This has been exemplified using an EpCAM-specific BiTE® antibody construct (Offner et al, 2006). The subsequent release of the pore-forming protein perforin and the apoptosis-inducing proteolytic enzyme granzyme B by T cells results in the induction of apoptosis in the target cells. AMG 562-mediated T-cell activation not only induces the directed release of cytotoxic proteins to target cells, but also results in a transient production of cytokines such as tumor necrosis factor (TNF), interferon gamma (IFN-γ), interleukin-2 (IL-2), and IL-6 by T cells in vitro. These in vitro studies also demonstrated that cytokine release by AMG 562-activated T cells is attenuated by corticosteroids, which is accompanied by a slight reduction in cytotoxic potency.

The anti-tumor activity of AMG 562 was evaluated in a mantle cell lymphoma xenograft model in non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice. In the orthotopic model NOD/SCID mice were intravenously injected with Granta-519 mantle cell lymphoma cells. Administration of AMG 562 at doses of 0.01, 0.1 or 1 mg/kg

every 5 days for a total of 3 IV bolus administrations resulted in a significant prolonged survival even at a dose of 0.01 mg/kg AMG 562.

2.2.2 Pharmacokinetics

Single-dose pharmacokinetics (PK) of AMG 562 was characterized after IV administration in cynomolgus monkeys. After a single IV bolus injection of 5 µg/kg, serum concentrations of AMG 562 declined in a biphasic manner with mean clearance (CL) values of 2.3 mL/hr/kg and a steady-state volume of distribution of 548 mL/kg. The mean half-life ($t_{1/2}$) of AMG 562 was 210 hours.

The repeat-dose PK of AMG 562 was also characterized in cynomolgus monkeys. AMG 562 was administered over 16 days of IV administration by 30-minute infusions. All animals received 5 µg/kg on day 1, and 25 µg/kg or 50 µg/kg on days 2, 5, 8, 11, and 14. The exposure of AMG 562 increased proportionally with increasing dose between the three dose groups. Concentrations of AMG 562 were measured in cerebral spinal fluid (CSF) at day 16 and were only detected in animals of the 50 µg/kg dose group. The mean concentration of AMG 562 in CSF was 354 pg/mL.

Based on allometric scaling of cynomolgus monkey PK, the predicted human terminal $t_{1/2}$ of AMG 562 is approximately 16 days.

2.2.3 Toxicology

The nonclinical safety assessment of AMG 562 was conducted in the cynomolgus monkey by IV administration and consisted of a 33-day repeat-dose GLP toxicology study. The cynomolgus monkey was selected as the toxicology species based on target binding affinity and bioactivity data (Investigator's Brochure). Intravenous administration in the cynomolgus monkey was chosen based on the intended clinical route of administration. Details of the AMG 562 nonclinical toxicology study are provided in the Investigator's Brochure.

In the GLP repeat-dose study AMG 562 was dosed either at 5 μg/kg on days 1, 5, 12, 19, and 26 (flat-dosing regimen) or at 5 μg/kg on day 1, followed by 50 μg/kg on days 5, 12, 19, and 26 (step-dosing regimen).. AMG 562 exposure was dose-proportional with evidence of accumulation by the end of the study.

Administration of AMG 562 was very well tolerated with no AMG 562-related mortalities, clinical observations or changes in body weight, food consumption, body temperature, respiratory rate, or neurologic, electrocardiographic, ophthalmologic, coagulation, or urinalysis parameters.

The results of the 33-day monkey toxicology study were consistent with the expected pharmacology of a CD19-targeting BiTE® antibody construct. Changes in response to the first IV dose of 5 μg/kg included decreased lymphocytes, with a complete depletion of circulating B cells that persisted until the end of the study. Serum cytokines, including monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and interferon gamma (IFN-γ) increased on day 1 with a minimal increase in MCP-1, particularly at 50 μg/kg on day 5. In addition, c-reactive protein (CRP) transiently increased 24 hours after dosing. In addition, serum globulin levels were decreased in animals of both AMG 562 dose groups at the end of the study on day 33.

At ≥ 5 μg/kg, microscopic changes in lymphoid tissue consisted of marked decreased cellularity of lymphoid follicles and germinal centers in both dose groups. Minimal to mild neutrophilic infiltration of the large intestine observed at ≥ 5 μg/kg was considered likely related to reduced local immunity secondary to AMG 562 pharmacology.

In conclusion, AMG 562-associated changes were generally consistent with the expected pharmacology of a CD19-targeting BiTE® antibody construct. None of the AMG 562-related changes in the GLP study were considered adverse. The highest non-severely toxic dose (HNSTD) was 5 μg/kg in the flat-dosing regimen and 5/50 μg/kg in the step-dosing regimen, respectively.

2.2.4 Dosing Experience With Other BiTE® Antibody Constructs

Bispecific antibody molecules, including bispecific T cell engager (BiTE®) antibody constructs, exert both unique and uniform mechanism of action independent of the respective targets, such that experiences with other BiTE® antibody constructs may be relevant for AMG 562.

Most clinical experience exists with blinatumomab (BLINCYTO®, AMG 103), a BiTE® antibody construct with specificity for CD3 and CD19, approved in multiple regions for

the treatment of Philadelphia chromosome-negative relapsed or refractory B cell precursor acute lymphoblastic leukemia. In clinical trials conducted for blinatumomab, the most commonly reported adverse reactions (≥ 20%) were infections, pyrexia, headache, infusion-related reactions, aanemia, febrile neutropenia/neutropenia, and thrombocytopenia (Blincyto® United States Prescribing Information). Additional adverse reactions, listed in regional prescribing information, included cytokine release syndrome (CRS), neurologic toxicities, tumor lysis syndrome (TLS), neutropenia/febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and pancreatitis. Preparation/administration errors have also occurred with blinatumomab treatment and is listed as a warning in the regional prescribing information.

2.3 Benefit-risk Assessment

At this time, there is no clinical experience with AMG 562 in humans. Based on biological possibility, nonclinical toxicity studies of AMG 562, and clinical safety experience with blinatumomab and other BiTE® antibody constructs in hematology, the important potential safety risks of AMG 562 include CRS, decreased immunoglobulins, neutropenia and neurologic events. Clinical signs and symptoms of CRS vital signs and other safety laboratories, will be monitored during the study and at the appropriate time points to ensure subjects' safety. Refer to Section 6.2.1.4.2 for specific recommendations regarding the mitigation and management of potential risk of CRS. Section 6.2.1.4.2 also provides treatment procedures for concomitant therapy for infections, including recommendations for antimicrobial prophylaxis for neutropenia and opportunistic infections.

Neutropenia and febrile neutropenia (including life-threatening cases), observed in patients receiving blinatumomab, were among the most common adverse reactions (≥ 20%) in blinatumomab clinical trials (Blincyto® Prescribing Information). Experiences with other CD19-targeted therapies for hematologic malignancies indicate the potential for neurotoxicity. AMG 562 is a BiTE® antibody construct with prolonged half-life targeting CD19, similar to blinatumomab, a BiTE® antibody construct also targeting CD19. A wide range of commonly-observed neurological symptoms have been associated with the use of blinatumomab, and among patients receiving blinatumomab, grade ≥ 3 neurologic events following initiation of blinatumomab administration included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders

(Blincyto® Prescribing Information). Neurologic toxicities have also been reported among patients receiving axicabtagene ciloleucel and tisagenlecleucel, both CD19-directed genetically modified autologous T cell immunotherapies indicated for the treatment of adult patients with relapsed or refractory large B cell lymphoma, including diffuse large B cell lymphoma (DLBCL) (Yescarta Prescribing Information, 2017; KYMRIAH prescribing information, 2018).

For a listing of important potential risks, see Table 3. Please refer to the AMG 562 Investigator's Brochure for further description of potential risks.

Table 3. Important Potential Risks of AMG 562

Potential Risk	Description
Cytokine Release Syndrome (CRS)	Non-antigen-specific toxicity occurring as a result of high-level immune activation (Lee et al., 2014) Signs and symptoms many include the following: • Constitutional – fever, rigors, fatigue, malaise • Neurologic – headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • Respiratory – dyspnea, tachypnea, hypoxemia • Cardiovascular – tachycardia, hypotension • Gastrointestinal – nausea, vomiting, transaminitis, hyperbilirubinemia • Hematology – bleeding, hypofibrinogenemia, elevated D-dimer • Skin – rash
Decreased Immunoglobulins	Decreases in circulating immunoglobulins secondary to depletion of B cells.
Neutropenia	Transient decreases in the number of circulating leukocytes, including neutrophils.
Neurologic Events	Neurological symptoms reported with the use of blinatumomab, a BiTE® antibody construct targeting CD19, included tremor, dizziness, encephalopathy, paresthesia, aphasia, and confusional state.

2.3.1 Key Benefits

For the proposed study, some participants in the dose escalation phase may derive benefit from AMG 562 during dose escalation. Based on the pharmacological activities and similarity to blinatumomab, it is expected that with the selected RP2D utilized for the expansion cohort more participants may benefit from AMG 562.

2.3.2 Key Risks, Identified and Potential, and Mitigations

Identified risks are untoward occurrences (eg, adverse events, laboratory, or radiographic abnormalities) that have been observed in subjects who have received AMG 562, and for which a causal relationship to AMG 562 has been established based

upon all available evidence. Potential risks are safety concerns based on mechanism of action, nonclinical data, or clinical data from similar compounds that have either not yet been observed in human subjects receiving AMG 562 or for which a causal association with AMG 562 has not yet been established.

There are currently no important identified risks for AMG 562. Based on the toxicology evaluation in cynomolgus monkeys and the known effects of other bispecific antibody molecules, including BiTE® molecules, the following are the important potential risks and proposed clinical monitoring strategies for AMG 562 (Table 4).

Table 4. Summary of Important Potential Risks of AMG 562

Safety Risks	Nonclinical Data for AMG 562	Clinical Data for Other BiTE® Molecules	Safety Monitoring
Cytokine release syndrome	AMG 562-related changes in clinical chemistry parameters in GLP toxicology study in cynomolgus monkeys consistent with an acute phase response, including increased cytokines (MCP-1, IL-6 and IFN-γ) on Day 1 (4 hours post-dose)	CRS observed in clinical trials evaluating other BiTE® molecules, including blinatumomab [1]	Monitoring of vital signs, hematology, comprehensive metabolic profiles and associated AEs Requirements for use of steroids, tocilizumab and monitoring of CRS Hospitalization and specific infusion interruption and stopping rules
Decreased immunoglobulins	Decreased globulins observed in GLP toxicology study in cynomolgus monkeys consistent with expected pharmacology (B cell depletion) of AMG 562	Decreased immunoglobulins observed in clinical trial evaluating blinatumomab among patients with relapsed/refractory ALL [2]	Monitoring of laboratory assessments, including serum immunoglobulins Guidance regarding infection prophylaxis and treatment per standard of care
Neutropenia	AMG 562-related changes in hematology parameters in GLP toxicology study in cynomolgus monkeys included decreased WBC counts, including neutrophils, with recovery by the end of the study	Neutropenia observed in clinical trials evaluating other BiTE® molecules, including blinatumomab [1]	Monitoring of vital signs, hematology parameters and associated AEs Subject eligibility criteria for hematology parameters Guidance regarding dose-holding and stopping rules pertaining to hematology parameters, including neutropenia, and infection prophylaxis and treatment of infections per standard of care
Neurologic events	AMG 562 detected in CSF without associated neurotoxicity in repeat-dose PK/PD study No AMG 562-neurological effects observed in GLP toxicology study in cynomolgus monkeys	Neurologic toxicities reported in association with other CD19-targeting drugs [1, 3]	Neurologic evaluations and monitoring of AEs Subject eligibility criteria for clinically relevant central nervous system pathology Guidance regarding dose reductions, infusion interruptions and stopping rules due to AEs

AE = adverse event; ALL = acute lymphoblastic leukemia; BiTE = bispecific T cell engager;
CRS = cytokine release syndrome;
CSF = cerebrospinal fluid; GLP = Good Laboratory Practice; IFN = interferon; IL = interleukin;
MCP = monocyte chemoattractant protein; WBC = white blood cell

[1] Blincyto® (blinatumomab) [US Prescribing Information]. Thousand Oaks, CA: Amgen Inc; 2017.
[2] Kantarjian H et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376:836-847.
[3] Yescarta (axicabtagene ciloleucel) [US Prescribing Information]. Santa Monica, CA: Kite Pharma Inc; 2017.

2.4 Rationale

BiTE® antibody constructs are designed to engage T cells to exert cytotoxic activity against cells targeted by surface expression of a selected antigen. BiTE® antibody constructs consists of 2 single chain variable fragment (scFv) binding domains, specific for a selected target antigen, eg an antigen expressed by malignant cells, and the epsilon subunit of the CD3 complex present on T cells. The cross-linking of the target antigen and CD3 antigen mediated by the BiTE® triggers target cell specific cytotoxicity closely resembling standard cytotoxic T lymphocyte activation.

AMG 562 is a BiTE® antibody construct that targets CD19 and is intended for the treatment of patients with B-cell malignancies. CD19 (Leu-12, CVID3, B4) is a transmembrane protein expressed on B-lineage cells and the majority of B-cell malignancies. It belongs to the immunoglobulin super family and forms a signaling complex with CD21, CD225 and CD81 (Bradbury, 1992; Katz and Herishanu, 2014). CD19 has been shown to contribute to B-cell receptor mediated signaling and defects in CD19 are associated with hypogammaglobulinemia with varying degrees of immunodeficiency (Conley, 2009).

CD19 has been used as a target in several different approaches to treat B-cell malignancies. The success of these novel therapies supports CD19 as a suitable target.

Relevant for AMG 562 is the clinical experience with the Bispecific T cell engager (BiTE®) antibody construct blinatumomab targeting CD19. Blinatumomab demonstrated clinical activity in acute lymhoblastic leukemia (ALL), administered as a continuous infusion, was granted approval in December 2014, for the treatment of relapsed and refractory B-cell precursor ALL .

Recently CD19 chimeric antigen receptor T (CAR-T)-cell therapies have been approved for the treatment of relapsed / refractory B-cell acute lymphoblastic leukemia (r/r B-ALL) (tisagenlecleucel) and relapsed / refractory diffuse large B-cell lymphoma (r/r DLBCL) (axicabtagene ciloleucel). Blinatumomab also showed signs of clinical activity in a phase 2 study in r/r DLBCL (Viardot et al., 2016) AMG 562, which also targets CD19 and engages T cells via CD3 binding, is a novel BiTE molecule intended to treat patients with B-cell malignancies such as relapsed / refractory non-Hodgkin lymphoma.
AMG 562 is a half-life extended (HLE) BiTE® antibody construct combining the binding specificities for CD19 and CD3 genetically fused to the N-terminus of a single chain IgG Fc (fragment crystallizable; scFc) region. The fusion to the Fc domain is a

well-established strategy to prolong the half-life of protein therapeutics. This key modification, designed to maintain very efficient CD19-dependent target cell killing, should permit administration as intermittent short IV infusions.The PK of AMG 562 in humans was estimated using allometric scaling of PK parameters obtained from nonclinical studies in cynomolgus monkeys at doses ranging between 5–50 µg/kg. In repeat-dose studies cynomolgus monkeys, evidence suggesting changes in CD19 abundance or saturation of CD19 binding was observed. As such, parallel linear and nonlinear clearance pathways were incorporated to characterize the AMG 562 PK from the pooled monkey data.

2.4.1 Dose Selection Rationale

The planned doses of AMG 562 in this study are 0.1, 0.3, [redacted]

AMG 562 human PK profiles and exposures were predicted using a 2-compartment model with parallel linear and non-linear elimination that accounts for observed non-linearity in AMG 562 PK following repeat-dose administration in cynomolgus monkeys. Human PK parameters were scaled using allometry from estimated PK parameters in cynomolgus monkey studies described in Section 2.2.2. Based on predicted AMG 562 PK, a starting dose of 0.1 µg following a clinical IV infusion (1 hour) is predicted to acheive maximum serum concentrations approximating the MABEL (in vitro concentration required for half-maximal effect [EC_{50}] of AMG 562-mediated autologous B cell depletion, 35.7 pg/mL). The use of the EC_{50} as the MABEL and basis for the FIH starting dose is supported by the previous and safe implementation of this strategy to identify the maximum recommended starting doses of previous bi-specific CD3-targeting molecules in clinical development while minimizing the number of dose escalations necessary to establish a maximum tolerated dose (Saber et al., 2017).

Additionally, relative to human exposure predictions at the starting dose, mean AUC_{168hr} and C_{max} exposures achieved at the highest non-severely toxic dose (HNSTD) of the flat-dose regimen of 5 µg/kg in the 33-day toxicology study in cynomolgus monkeys were approximately 1800-fold and 320-fold greater than human AUC_{168hr} and C_{max} exposures predicted at the 0.1 µg starting dose, respectively, after correction for a 17-fold potency difference in human and cynomolgus monkey effector cells. Of note, relative to the step-dose regimen of 5 µg/kg followed by a step up to 50 µg/kg (5/50 µg/kg) also

evaluated in the 33-day toxicology study, AUC_{168hr} and C_{max} exposures were approximately 20000-fold and 3400-fold greater than human exposure predictions, after a 17-fold potency correction.

Subsequent planned escalations in AMG 562 dose up to [redacted] µg are shown in Table 5. At the highest planned clinical dose of [redacted] µg, the ratio of mean AUC_{168hr} and C_{max} exposures achieved at the 5 µg/kg HNSTD in the 33-day toxicology study in cynomolgus monkeys and predicted human AUC_{168hr} and C_{max} exposures were approximately [redacted] respectively, after a 17-fold potency difference in human and cynomolgus monkey effector cells (ratio of mean AUC_{168hr} and C_{max} exposures achieved at the 5/50 µg/kg HNSTD in the 33-day toxicology study were approximately [redacted], respectively, after potency correction).

Table 5. First-in-human Doses and Predicted Exposure Margins (Potency Adjusted) From the Pivotal Repeat-dose Intravenous Toxicity Study of AMG 562 in the Cynomolgus Monkey

AMG 562 IV Dose Q1W (µg)	Predicted Human Exposures[a]		Potency-corrected Predicted Exposure Margins (HNSTD = 5 µg/kg)[b]		Potency-corrected Predicted Exposure Margins (HNSTD = 5/50 µg/kg)[b]	
	AUC_{168h} (h·ng/mL)	C_{max} (ng/mL)	AUC_{168h}[c] (h·ng/mL)	C_{max}[c] (ng/mL)	AUC_{168h}[c] (h·ng/mL)	C_{max}[c] (ng/mL)
0.1	0.41	0.03	1800	320	20000	3400
0.3	1.2	0.1	600	110	6500	1100
[redacted]						

AUC_{168h} = area under the concentration-time curve from 0 to 168 hours; C_{max} = maximum observed concentration in a dosing interval; GLP = good laboratory practices; HNSTD = highest non-severely toxic dose; IV = intravenous; Q1W = once a week.

[a] Predicted human exposures at steady state (based on free serum AMG 562 concentrations) following once-weekly AMG 562 dosing for 4 weeks (Investigator's Brochure).

[b] Predicted exposure margins were calculated as follows: $(AUC_{168h,cyno,day\ 26} / AUC_{168h,human,SS}) \div 17$; $(C_{max,cyno,day\ 26} / C_{max,human,SS}) \div 17$; where 17 is a correction for a 17-fold difference in AMG 562 potency between human and cynomolgus monkey effector cells in an autologous B cell depletion assay (Investigator's Brochure).

[c] The average AUC_{last} and C_{max} observed in the GLP toxicology study on day 26 at the HNSTD (5 µg/kg) were 12.6 hr·µg/mL and 0.182 µg/mL. At the step-dosing HNSTD of 5/50 µg/kg the average AUC_{last} and C_{max} were 137 hr·µg/mL and 1.88 µg/mL (Investigator's Brochure).

Minimally efficacious exposures of AMG 562 were estimated based on the predicted human AMG 562 PK, the evaluation of nonclinical assessments of AMG 562 activity and clinical concentrations of blinatumomab, a CD19-targeting bispecific T cell engager, that were associated with response in NHL patients. Based on the in vitro assessment of individual dose-response curves of autologous B cell depletion from 16 different donors, a mean EC_{90} of 125 pg/mL was calculated. An AMG 562 dose of [redacted] µg is predicted to provide trough coverage of the EC_{90} following once weekly administration and is expected to achieve pharmacological response. Clinical experience from blinatumomab in NHL patients was also used to inform efficacy predictions of AMG 562. In a phase 2 study in NHL patients, exposure to blinatumomab at a dose of 112 µg/day for at least one week appeared to be required for efficacy (overall response rate [43%]; complete response [19%]; Viardot et al., 2016). Correcting for the differences in CD19 affinities between AMG 562 and blinatumomab, an AMG 562 dose of [redacted] µg is expected to provide trough coverage of the equivalent blinatumomab exposure associated with complete response.

Collectively, minimally efficacious exposures of AMG 562 are predicted at doses ranging between [redacted] µg, following once weekly administration.

2.5 Clinical Hypotheses

The following hypotheses will be tested with this clinical protocol.

- At least one dose level of AMG 562 administered by IV infusion is expected to achieve acceptable safety and tolerability in subjects with relapsed and/or refractory DLBCL, MCL, or FL.
- A favorable PK profile will be achieved with AMG 562 administered by IV infusion.
- Objective responses will be observed at a dose level that achieves acceptable safety and tolerability.

3. EXPERIMENTAL PLAN

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 [redacted]

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 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 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 PD of different doses of AMG 562 in subjects with relapsed/refractory DLBCL, MCL or FL using a Bayesian logistic regression model (BLRM; Neuenschwander et al, 2008). AMG 562 will be administered as IV infusions at weekly intervals. Based on emerging trial data, step-dosing may be recommended by the DLRT if required to mitigate initial AEs (step-up dosing). Step-up dosing includes a lower dose for the 1st infusion on Day 1 of the treatment followed by escalation to the "target dose" on all subsequent dosing days. The highest dose for the 1st infusion on Day 1 is defined as initial dose. The highest dose following step-up

dosing is defined as the target dose. Additional dose steps may be administered subsequently at daily intervals. After administration of the target dose, treatment will continue with weekly administrations of AMG 562 at the target dose. Planned dose levels (dose per infusion) for the dose exploration cohorts are as follows: 0.1 µg, 0.3 µg, [redacted].

If the preliminary MTD is not reached within the pre-planned dose range, doses > 1000 µg may be investigated by submission of a protocol amendment to the competent authorities for review. If no DLTs are observed, the dose escalation will continue to the next planned dose level as per Part 1 Study Design and Schema in the study protocol. When enrollment is completed for each cohort (single and multiple subject), the DLRT will convene at the end of the DLT evaluation period and review all available safety, PK and pharmacodynamic data. The DLRT will provide the recommendation to proceed with dosing of patients in the next cohort.

Dose escalation/de-escalation recommendations will be guided by the BLRM model of dose toxicity and evaluation of all available safety data, laboratory, and PK information. If two or more subjects experience a DLT at a dose level, enrollment to the cohort will be terminated and dose de-escalation may occur. If late onset adverse events occur during a cohort, the DLRT may adaptively re-consider the doses evaluated within a cohort for subsequent dosing and/or possibly trigger a de-escalation or withholding of additional doses in subsequent cohorts. Based on the BLRM model and after reviewing all available safety and tolerability data, the DLRT will make dose escalation/de-escalation recommendations. Subjects may continue to receive AMG 562 until evidence of disease progression, unacceptable toxicity or withdrawal of consent.

In addition to the dose, the DLRT may recommend changing the dosing schedule (eg, dosing interval) for subsequent cohorts. The DLRT may also recommend to prolong the DLT window or to include step-up dosing for future cohorts based on observed tolerability and other clinical signs, pharmacological and PD results.

Dose exploration will be conducted in 2 stages using the 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. Once higher dose levels are open for enrollment or any of the safety criteria listed below are observed, multiple subject cohorts of 3 to 4 subjects per cohort will open for enrollment. Enrollment of subjects at each dose level in the multiple subject cohorts will be staggered by at least 3 days.

The switch from single to multiple subject cohorts will be triggered 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

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. The dose escalation for subsequent cohorts 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 DLT evaluation period will be 28 days for all cohorts. The DLT evaluation period may also be extended to assess events starting within the DLT window in case the DLT definition is time dependent. 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 is seen more frequently, or is more severe than expected, or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the 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.

Premedication for Cycle 1: an 8 mg dose of IV or PO dexamethasone approximately 1 hour prior to the start of the AMG 562 infusion is mandatory:

- Prior to each infusion in Cycle 1 8 mg dexamethasone IV or PO as premedication

Premedication for Cycle 2 and beyond:

- Pre medication with 8 mg IV or PO dexamethasone for each subsequent cycle will be required for any subject who experienced grade ≥ 2 neurotoxicity or grade ≥ 2 CRS in the preceding cycle

If CRS and neurotoxicity of grade 2 or higher did not occur in the prior cycle(s), premedication with dexamethasone can be reduced to 4 mg. If subjects tolerate AMG 562 well with reduced dose dexamethasone, premedication with dexamethasone can be discontinued for the next cycle in consultation with Amgen Medial Monitor

No additional premedication is permitted on the trial. If the evaluation of available safety and laboratory data suggests that adjustment to the dexamethasone schedule are required or additional premedication is necessary, the DLRT can recommend to adjust the current schedule and/or add additional premedication, eg, antihistamines and H2 blockers to the premedication regimen. In this case all future cohorts will receive this additional premedication. All subjects will be pre-treated unless a contraindication for this premedication exists.

Once the dose exploration has provided a RP2D, tocilizumab may be evaluated as an alternative prophylaxis to prevent/reduce severity of CRS. A cohort of three patients may be treated with AMG 562 at the RP2D dose level and a single dose of 400 mg IV tocilizumab will be administered approximately 15 minutes prior to the day 1 dose of AMG 562 replacing pretreatment with dexamethasone. If no DLTs are observed three additional patients will be included in this cohort. The use of tocilizumab may be further explored based on observed tolerability and other clinical and pharmacological data.

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

Step-up dosing will be explored to prevent first dose effects that have been observed with other BiTE antibodies namely CRS, neurologic events and TLS. It will be introduced when two or more DLTs consistent with CRS, neurologic events and TLS are observed in one cohort. The DLRT may recommend introducing step-up dosing earlier when 2 or more grade ≥1 CRS events (as referenced by Lee et al, 2014) or 2 or more grade ≥1 neurologic events are observed in one cohort. For single patient cohorts the DLRT may introduce step-up dosing earlier when 2 or more grade ≥ 1 CRS or neurologic events are observed in 2 consecutive cohorts. The decision for CRS related events should be supported by confirmation of the clinical diagnosis with evaluation of all available clinical and laboratory parameters including observation of elevated cytokine

levels and / or elevated levels of other markers of inflammatory reactions consistent with CRS and excluding other causes for the observed symptoms.

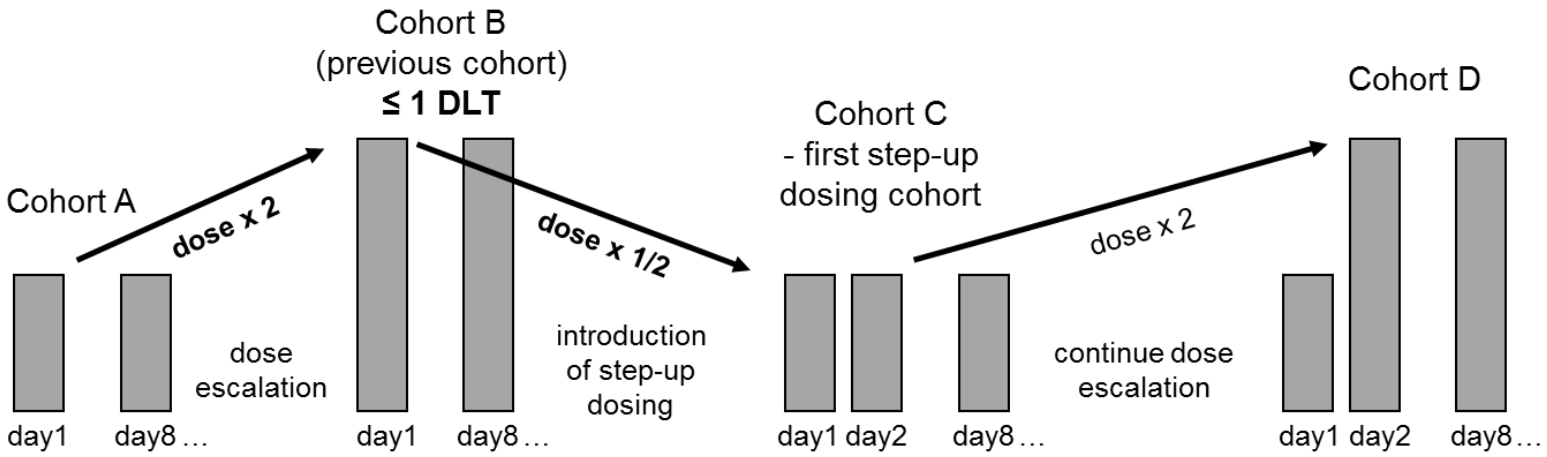
With step-up dosing, the dose of the first infusion on treatment day 1 (initial dose) will be lower than the dose of the infusion on day 2 (target dose). The target dose will be administered subsequently at weekly intervals starting on Day 8. Additional dose steps may be implemented based on tolerability as observed in the clinical and pharmacological data. If additional dose steps are applied, the initial dose on day 1 will be followed by 1, 2, or 3 stepwise increasing intermediate doses at one-day intervals. Following the last intermediate dose, with again a one-day interval, the highest dose (target dose) is administered. Administration of the target dose then continues at weekly intervals starting on Day 8 (see Figure 1 with an example of dosing without step-up dosing; Figure 2 and Figure 3 with possible variants of step-up dosing).

To establish doses for the step-up dosing, dose selection will be performed as follows:

Step-up dosing may be introduced after observation of adverse events in the cohort before introduction of step-up dosing (hereafter referred to as previous cohort). Two scenarios are differentiated depending on the frequency and severity of adverse events: scenario A with one or no DLTs in the previous cohort and scenario B with two or more DLTs in the previous cohort. Two sub-scenarios are differentiated depending on the dose escalation that determined the dose for the previous cohort: scenarios A1 and B1 with two-fold dose escalation and scenarios A2 and B2 with three-fold dose escalation.

Scenario A1:

- one or no DLTs in the previous cohort
- two-fold dose escalation for previous cohort
- dose for step-up dosing on days 1 and 2 will be half the dose of the previous cohort

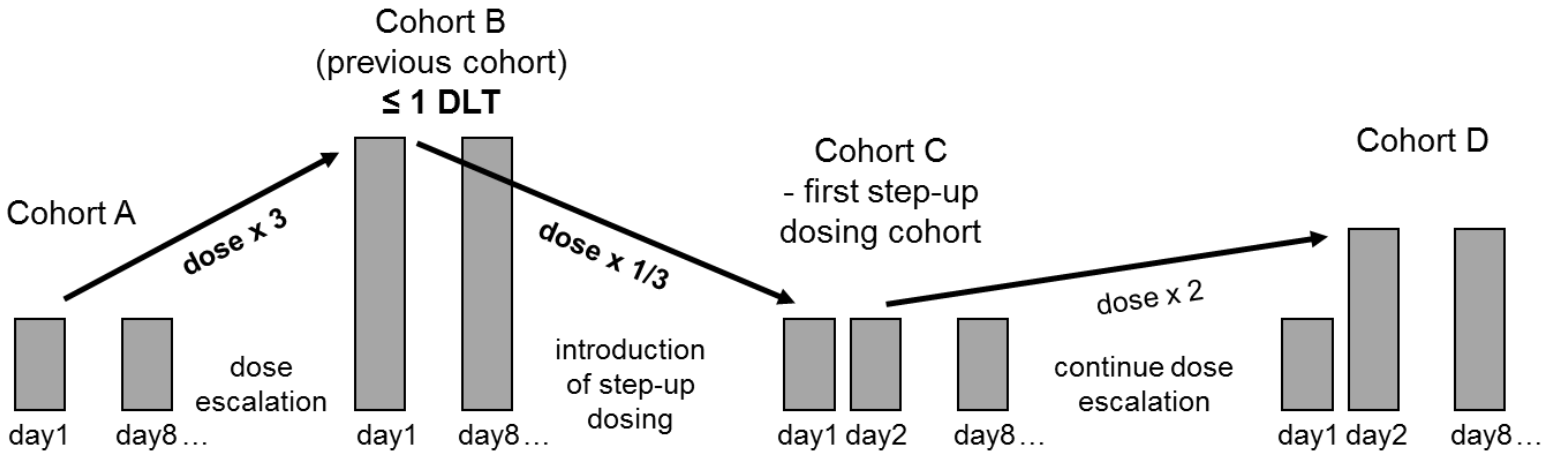


Example for possible dosing in Scenario A1:

Cohort A			Cohort B			Cohort C			Cohort D		
day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8
[redacted]µg	-	[redacted]µg	[redacted]µg	-	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg

Scenario A2:

- one or no DLTs in the previous cohort
- three-fold dose escalation for previous cohort
- dose for step-up dosing on days 1 and 2 will be a third of the dose of the previous cohort

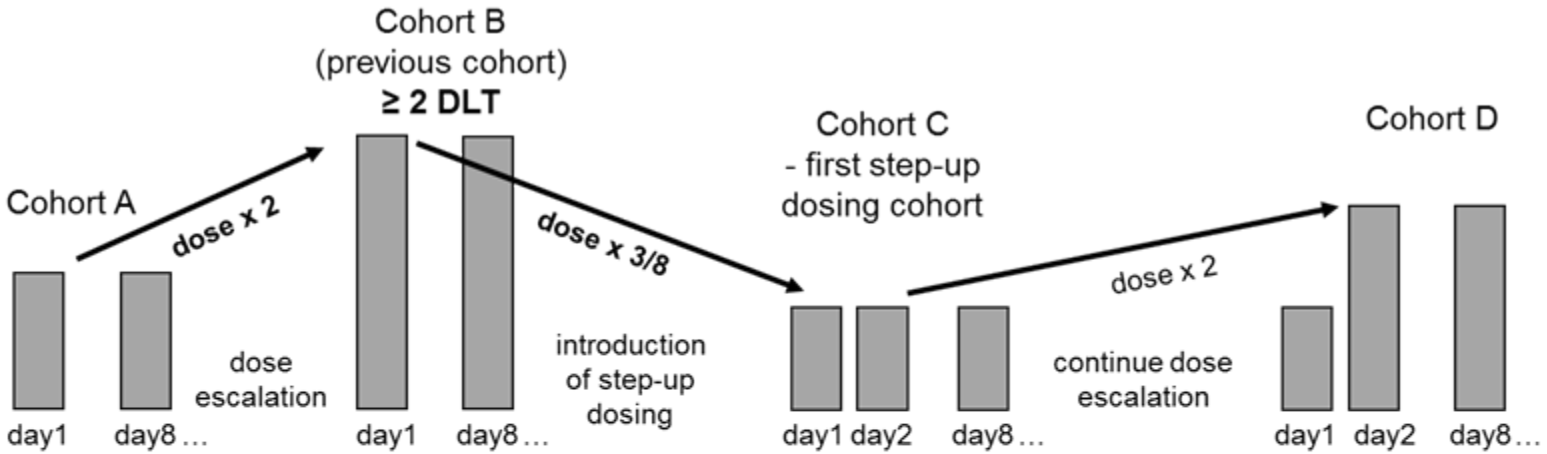


Example for possible dosing in Scenario A2:

Cohort A			Cohort B			Cohort C			Cohort D		
day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8
[redacted]µg	-	[redacted]µg	[redacted]µg	-	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg

Scenario B1:

- two or more DLTs in the previous cohort
- two-fold dose escalation for previous cohort
- dose for step-up dosing on days 1 and 2 will be 3/8th of the dose of the previous cohort

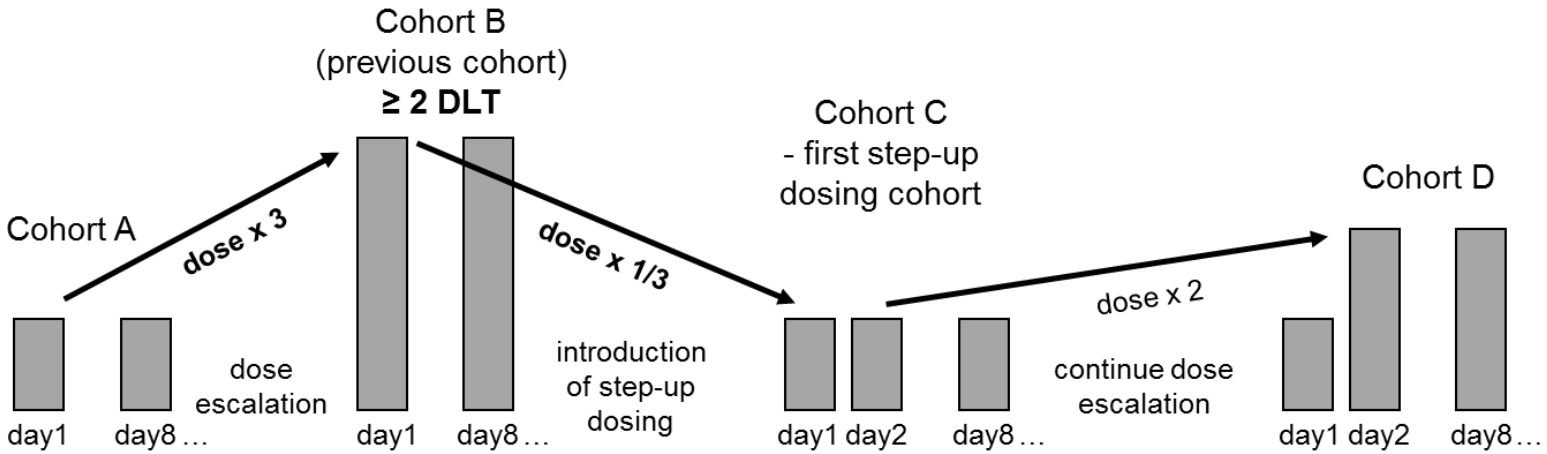


Example for possible dosing in Scenario B1:

Cohort A			Cohort B			Cohort C			Cohort D		
day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8
[redacted]µg	-	[redacted]µg	[redacted]µg	-	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg	[redacted]µg

Scenario B2:

- two or more DLTs in the previous cohort
- three-fold dose escalation for previous cohort
- dose for step-up dosing on days 1 and 2 will be a third of the dose of the previous cohort



Example for possible dosing in Scenario B2:

Cohort A			Cohort B			Cohort C			Cohort D		
day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8	day 1	day 2	day 8
[redacted] µg	-	[redacted] µg	[redacted] µg	-	[redacted] µg	[redacted] µg	[redacted] µg	[redacted] µg	[redacted] µg	[redacted] µg	[redacted] µg

In subsequent cohorts the dose to be administered at the step on day 2 will be escalated by two-fold dose increases until a DLT is observed. If a DLT is observed, the target dose for the step on day 2 for the following cohorts will be estimated using the BLRM, until an MTD (MTD for target dose) is reached.

In case a second dose step is implemented on day 3, the intermediate dose on day 2 will be at or below the MTD for day 2. The MTD for the target dose of the dose step on day 3 will be established in the same manner as described above for the MTD for day 2. In the first cohort to establish the dose on day 3, subjects will receive the established initial dose on day 1. The intermediate dose on day 2 and the dose for day 3 will be determined according to the scenarios A1 to B2 described above but based on the dose and dose increment of day 2 of the previous cohort. In subsequent cohorts the dose to be administered at the step on day 3 will be escalated by two-fold dose increases until a DLT is observed. If a DLT is observed, the target dose for the step on day 3 for the following cohorts will be estimated using the BLRM, until an MTD (MTD for target dose) is reached.

Potential further step doses will be established in a similar manner.

The DLRT may recommend prolonging the dosing intervals for the step-up dosing for future cohorts to 2, 3, or 4 days. Other changes of the step-up dosing intervals will be introduced by an amendment to the protocol.

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.

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 added 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 after the first 15 subjects are enrolled and have had the opportunity to receive at least five weeks of treatment (with recruitment ongoing). Additionally, the DLRT will review safety data in the expansion part, after the first 10 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. Ad hoc meetings may be convened at any time by the DLRT to review the safety data if deemed necessary. The overall study design is described by the Part 1 and Part 2 Study Design and Schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1

3.2 Number of Sites

The study will be conducted at approximately 15-20 sites in Belgium, Canada, Germany, Japan, South Korea and the United States. Additional sites and countries may be added.

Sites that do not enroll subjects into an open cohort within 6 months of site initiation during dose exploration, or within 3 months of site initiation during the expansion part of the study, respectively, may be closed or replaced.

3.3 Number of Subjects

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

Overall, up to approximately 85 subjects may be enrolled in the study. Up to 30 subjects will be enrolled in the dose exploration Part 1. Up to 55 subjects will be enrolled into the dose expansion Part 2.

Once targeted enrollment for the expansion cohort is complete, investigators will be informed in writing. Once this information is sent, potential subjects should not start consenting/screening process For ethical and operational reasons subjects who already are in the screening phase at the time of enrollment completion for a specific group will still be allowed to be treated. Therefore, an over running of subject recruitment might be possible. Based on emerging data, additional subjects may be enrolled.

The rationale for the number of subjects is detailed in Section 10.2.

3.4 Replacement of Subjects

Ineligible subjects (ie, subjects who were exposed to investigational product but post hoc were found to be ineligible) may be replaced.

Subjects enrolled in Part 1 may be replaced if they are not evaluable for DLT. Subjects will NOT be considered DLT evaluable if:

- the subject did not receive study treatment
- the subject missed 2 consecutive doses out of the 4 planned doses for reason(s) other than DLT during the DLT evaluation period
- the subject ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT.

Exception to this rule is:

Discontinuation of treatment due to early progression after receiving at least 3 doses of investigational product and safety follow-up data for entire DLT evaluation period are available.

All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRT recommendations.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to 2 years.

This includes a screening period lasting up to 21 days, a treatment period lasting for a median of approximately 8 months, a Safety follow-up visit 30 (+7) days after the last dose of AMG 562, and a follow-up period lasting up to 2 years from the first dose of AMG 562.

The actual duration for individual subjects will vary depending upon tolerability of AMG 562, evidence of clinical progression, and willingness to participate in the study. End of study (EOS) for an individual subject is defined as the date of the final study visit

3.5.2 End of Study

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

The primary analysis for the dose exploration part will occur when target enrollment is complete and each subject either completes 3 months on study or withdraws from the study. The primary analysis for the dose expansion part will occur when targeted

enrollment is complete and each subject has the opportunity to receive at least 3 months of treatment at target dose. If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study (EOS) date is defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, LTFU),

4. SUBJECT ELIGIBILITY

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

4.1 Inclusion Criteria

A subject that has provided written informed consent may be eligible for inclusion in this study only if the following criteria are met.

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

102. Age ≥ 18 at the time of informed consent

103. Biopsy proven B-NHL including:

- **DLBCL**, which also includes DLBCL that represents transformation of indolent NHL (including follicular, marginal zone, and lymphoplasmacytic lymphoma excluding chronic lymphocytic leukemia or Hodgkin Lymphoma) and DLBCL with alterations of MYC and BCL2 and/or BCL6 also described as double-hit and triple-hit lymphomas.
- **FL**
- **MCL**

Presentations of these histologies with substantial occurrence of malignant cells into the bloodstream (lymphocyte count ≥ 7 x 10^9/L) including all leukemic presentations are excluded.

The following histologies are not eligible:

Lymphoblastic lymphoma

Burkitt lymphoma

Any histologies not specifically mentioned must be discussed with the Medical Monitor

- Subjects with transformation of indolent lymphoma must have received therapy after a diagnosis of transformation that is appropriate for aggressive histology as described in 105.
- Subjects who received prior CD19-targeting treatment are allowed (CAR-T cell therapy is excluded) . A biopsy following CD19-targeting treatment is required unless no lesions are accessible or the risk of the biopsy is deemed too high by the investigator

104. For Part 2 (Expansion in patients with DLBCL): only biopsy proven DLBCL (biopsy proven at least at primary diagnosis), including DLBCL that represents transformation of indolent NHL (including follicular, marginal zone, and lymphoplasmacytic lymphoma excluding chronic lymphocytic leukemia or Hodgkin Lymphoma) are eligible. Other histologies are not eligible.
    - Presentations of these histologies with substantial occurrence of malignant cells into the bloodstream (lymphocyte count ≥ 7 x 10^9/L) including all leukemic presentations are excluded.
    - Subjects with transformation of indolent lymphoma must have received therapy after a diagnosis of transformation that is appropriate for aggressive histology as described in 105..
    - Subjects who received prior CD19-targeting treatment are allowed (CAR-T cell therapy is excluded) A biopsy following CD19-targeting treatment is required unless no lesions are accessible or the risk of the biopsy is deemed too high by the investigator
105. For DLBCL: Refractory (no prior **CR**/CMR) to first or later line of treatment or relapsed (prior CR/CMR) after two or more prior treatments, with at least one treatment consisting of standard multiagent chemotherapy containing an anthracycline AND an approved anti-CD20 agent. Examples of appropriate therapy include but are not limited to R-CHOP (14 or 21), R-CHOEP, and DA-R-EOCH.
    For FL: Refractory (no prior CR/CMR) to first or later line of treatment or relapsed (prior CR/CMR) after three or more prior treatments, with at least one treatment consisting of a standard chemotherapy containing an approved anti-CD20 agent. Examples of appropriate therapy include but are not limited to R-CHOP, R-CVP, and BR.
    For MCL: Refractory (no prior CR/CMR) to first or later line of treatment or relapsed (prior CR/CMR) after three or more prior treatments, with at least one treatment consisting of a standard chemotherapy containing an approved anti-CD20 agent. Examples of appropriate therapy include but are not limited to R-CHOP, BR and hyper-CVAD alternating with R-MTX/Ara-C.
    For subjects with refractory B-NHL and who have received radiotherapy, PET positivity should be demonstrated no less than 6 weeks after the last dose of radiotherapy
106. Minimum life expectancy of 12 weeks

107. Radiographically measurable disease with a clearly demarcated nodal lesion at least 1.5 cm in its largest dimension or a target extranodal lesion at least 1.0 cm in its largest dimension. In the dose exploration phase in case disease is not radiographically measurable PET positivity (ie, Deauville ≥4) instead is acceptable.

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

109. Laboratory parameters (completed within 14 days prior to enrollment):

    Hematology:

    - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
    - Platelets ≥ 75 x 10^9/L

    Chemistry:

    - Creatinine clearance ≥ 60 mL/min (calculated **using Cockcroft Gault equation**)
    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 3X upper limit of normal (ULN)
    - Total bilirubin (TBL) < 2x ULN (unless Gilbert's disease or if liver involvement with lymphoma)

4.2 Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

201. Treatment within 30 days prior to enrollment with another investigational device or drug (interventional clinical study / studies). Other investigational procedures while participating in this study are excluded (observational studies are permitted)

202. Prior anti-cancer therapy as specified below:

    - At least 6 weeks must have elapsed since any prior systemic inhibitory/stimulatory immune checkpoint molecule therapy (eg, ipilimumab, nivolumab, pembrolizumab, atezolizumab, OX40 agonists, 4-1BB agonists, etc) before the first dose of AMG 562
    - Other targeted anti-cancer therapy (chemotherapy, molecular targeted therapy, steroids) within 14 days or 5 half lives (which ever is longer) prior to first dose of AMG 562. Patients requiring continued treatment due to aggressive disease may only be included if there is agreement by both the investigator and the Amgen Medical Monitor.
    - Radiation therapy completed within 28 days prior to first dose of AMG 562
    - Autologous HSCT within six weeks prior to start of AMG 562 treatment
    - At least 4 weeks must have elapsed since any prior treatment with antibody therapy (exception immune checkpoint inhibitors) before the first dose of AMG 562

203. Prior CD19-directed CAR-T cell therapies

204. Prior allogeneic HSCT

205. For Part 2 (Expansion in patients with DLBCL): fluorodeoxyglucose non-avid patients

206. Baseline electrocardiogram (ECG) QTc > 470 msec

207. Autoimmune disorders requiring chronic systemic steroid therapy or any other form of immunosuppressive therapy. Patient may be included if the treatment is discontinued more than 3 months prior to the first dose of AMG 562 at a low likelihood of relapse AND if there is agreement by both the investigator and the Amgen Medical Monitor.

208. Unresolved toxicity from prior anti-tumor therapy, defined as not having resolved to CTCAE version 4.0 grade 1, or to levels dictated in the eligibility criteria with the exception of alopecia or toxicities from prior anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 28 days) which may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and the Amgen Medical Monitor

209. Presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, paresis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

210. Evidence of CNS involvement by NHL

211. Known infection with human immunodeficiency virus (HIV)

212. Exclusion of hepatitis infection based on the following results and/or criteria:

- Positive for hepatitis B surface antigen (HBsAg) (indicative of chronic hepatitis B or recent acute hepatitis B).
- Negative HBsAg and positive for hepatitis B core antibody: Assay for hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
- Positive Hepatitis C virus antibody (HCVAb): Assay for hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C

213. History of malignancy other than B-NHL within the past 3 years with the exception of:

- Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated cervical carcinoma in situ without evidence of disease
- Adequately treated breast ductal carcinoma in situ without evidence of disease
- Prostatic intraepithelial neoplasia without evidence of prostate cancer
- Adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

214. Major surgery within 28 days of first dose AMG 562

215. History of arterial thrombosis (eg, stroke or transient ischemic attack) within 12 months of first dose of AMG 562

216. Presence of fungal, bacterial, viral, or other infection requiring IV antimicrobials for management within 7 days of first dose AMG 562

    NOTE: Simple UTI and uncomplicated bacterial pharyngitis are permitted after consultation with sponsor and if responding to active treatment

217. Subject has known sensitivity to immunoglobulins or any of the products or components to be administered during dosing.

218. Males and females of reproductive potential who are unwilling to practice highly effective method(s) of birth control while on study through 110 days (females) and 170 days (males) after receiving the last dose of study drug. Highly effective methods of birth control include sexual abstinence (males, females); vasectomy; bilateral tubal ligation/occlusion; or a condom with spermicide (males) in combination with hormonal birth control or intrauterine device (IUD) (females)

219. Females who are lactating/breastfeeding or who plan to breastfeed while on study through 110 days after receiving the last dose of study drug

220. Females with a positive pregnancy test

221. Females planning to become pregnant while on study through 110 days after receiving the last dose of study drug

222. Males who are unwilling to abstain from sperm donation while on study through 170 days after receiving the last dose of study drug

223. Subjects likely to not be available to complete all protocol- required study visits or precedures including BM aspirates/biopsies, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

224. History or evidence of any other clinically-relevant concurrent disorder, condition or disease (eg, symptomatic congestive heart failure, unstable angia pectoris, cardiac arrythmia requiring therapy at time of screening) with the exception of those outlined above that, in the opinion of the investigator or Amgen Medical Monitor, if consulted, would not pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

5. SUBJECT ENROLLMENT

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

A subject is considered enrolled when the Investigator decides that the subject has met all eligibility criteria. The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined when the subject signs the informed consent form) receives a unique subject identification number before any study procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 445). The next 5 digits will represent the country code and site number (eg, 66001) and will be identical for all subjects at the site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at site 66001 will receive the number 44566001001, and the second subject at the same site will receive the number 44566001002.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

Subjects who do not meet all eligibility criteria may be rescreened up to 2 times at the discretion of the Investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 21 days of enrollment. Subjects who are determined not eligible after rescreen must be screen-failed and the reason for the screen-failure provided. Subjects may only be enrolled once into this study.

Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to the sponsor or designee. The Amgen representative will acknowledge receipt and return confirmation of dose cohort (dose exploration part) or group (dose expansion part), respectively, to the site.

5.1 Treatment Assignment

An Amgen representative will notify the site(s) in writing when a dose cohort (dose exploration part) or the dose expansion part, respectively, are open to screen and enroll new subjects. The treatment assignment date is to be documented in the subject's medical record.

6. TREATMENT PROCEDURES

6.1 Classification of Products, and/or Medical Devices

The Amgen Investigational Product (IP) used in this study is AMG 562.

Other protocol-mandated medication (eg, dexamethasone used for pre-dose treatment or for treatment of adverse events) are commercially available and are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-specified therapies.

6.2 Investigational Product

The investigational product will be administered at the research facility by a qualified staff member.

A physician or nurse trained in emergency medicine must be available at the time of administration of investigational product for immediate intervention in case of complications.

6.2.1 Amgen Investigational Product AMG 562

AMG 562 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures. AMG 562 will be supplied as lyophilized drug product in glass vials.

6.2.1.1 Dosage, Administration, and Schedule

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 562. AMG 562 will be delivered using infusion pumps (for the higher doses) and syringe pumps (for the lower doses)respectively, which are approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 562 solution for infusion will be prepared in bags for IV infusion and delivered intraveneously. AMG 562 may be administered through a peripheral venous line or a central venous access if available. The drug should not be administered as a bolus. Details on the dose calculation, preparation, and administration are provided in the IPIM.

The duration of infusion will be [redacted] for all doses. The DLRT may recommend to modify infusion rates based on emerging PK and safety. Changes to the infusion rate will not be less than 1 hour and will apply to all subjects of the same dose cohort. Please note: for infusion delays due to related adverse events, the instructions in Section 6.2.1.4.2 apply.

For further details on planned dosing see Section 3.1.

The planned dose levels for the dose exploration cohorts are shown in Part 1 Study Design and Schema. In the expansion part, the estimated MTD/RP2D and dosing schedule from the dose exploration part of the study will apply to all groups. For each group, a BLRM design may be used to update the estimate of the RP2D/MTD (see Section 3.1 for details).

Treatment can be administered as long as the subject is deriving benefit in the judgment of the investigator, unless 1 of the criteria for permanent discontinuation of treatment are met (see Section 6.2.1.4). In no case may treatment be continued beyond the end of the LTFU period of the last subject in the study.

Minimum hospitalization times for subjects will be as follows:

Without step-up dosing:

- 72 hours after infusion at C1D1 and C1D8
- 48 hours after infusion at C1D15 and C1D22 if there are no adverse events grade ≥1 up to day 15, otherwise 72 hours.
- For all subsequent infusions subjects should be monitored in hospital or outpatient clinic for at least 4 hours after start of each infusion with hospitalization at the discretion of the investigator

With step-up dosing:

- 72 hours after infusion at day 1, after every step dose infusion and for the first two infusions at target dose (similar to C1D1 and C1D8 without step-dosing)
- 48 hours after the 3rd and 4th infusion at target dose if there are no adverse events grade ≥ 1, otherwise 72 hours.
- For all subsequent infusions, subjects should be monitored in hospital or outpatient clinic for at least 4 hours after start of each infusion with hospitalization at the discretion of the investigator

In case of intra-subject dose escalation, subjects will be hospitalized as per the guidance for treatment initiation.

The DLRT may recommend changes in hospitalization requirements after review of available safety data. The hospitalization period for individual subjects may be extended at the discretion of the investigator. Any shortening of hospitalization period can only be implemented with the official approval of a substantial amendment of the protocol.

Study sites must have immediate access to a medical intensive care unit staffed by critical care providers. Prior to hospital discharge, vital signs will be measured in order to detect possible signs and symptoms of infusion reactions or CRS. If required for

logistical reasons (eg, long travel times), subjects may be hospitalized the day before start of dosing, as well as during the treatment period for required PK samples.

The start time of infusion should be chosen carefully so as to avoid any interference or inconvenience with time points of safety assessments or PK/pharmacodynamic measurements.

The planned dose, quantity administered (amount and concentration), start date/time, stop date/time, and lot number of investigational product are to be recorded on each subject's electronic case report form (eCRF).

6.2.1.2 Overdose

The effects of overdose of this product are not known. The administered AMG 562 dose may be up to 10% lower or higher than specified in the protocol. A dose of up to 10% higher than the intended dose may not require specific intervention.

In any case of overdose, consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen Medical Monitor is also strongly recommended even if there are no adverse events, in order to discuss further management of the subject. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved or returned to baseline and the adverse event(s) should be recorded/reported per Section 9.2.2.2.

6.2.1.3 Dose Limiting Toxicities (DLTs)

The DLT window (ie, DLT evaluable period) will start on Day 1 (start of the administration of the first infusion). The duration of the DLT window is 28 days from infusion Day 1.

The DLT window may also be extended to assess events starting within the window in case the DLT definition is time dependent.

See Section 3.4 for description of DLT evaluability and replacement of subjects.

All available safety data for subjects who are not DLT evaluable will still be evaluated and considered in DLRT recommendations.

A DLT will be defined as any of the events described below occurring in a subject during the DLT window unless clearly attributable to causes other than AMG 562 treatment. The CTCAE version 4.0 (see Appendix A) will be used to assess toxicities/adverse

events with the exception of CRS and tumor lysis syndrome (TLS). See Section 6.2.1.4 and Appendix K for grading criteria of CRS, neurotoxicity and TLS respectively.

1. Death not clearly due to the underlying disease or extraneous causes.
2. Any subject meeting the criteria for Hy's Law case (ie, severe drug-induced liver injury [DILI]) will be considered a DLT. A Hy's Law case is defined as: AST or ALT values of ≥ 3x ULN AND with serum total bilirubin (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 (see Section 6.4 for hepatotoxicity management and Appendix A for further explanation of Hy's law case and Management of Hepatic Function)
3. Non-hematologic DLTs:
   - Non-hematological adverse event grade 3 or higher, **EXCEPT**:
     - infection responding to antibiotic/anti-infective treatment within 48 hours
     - grade 3 fatigue or asthenia
     - grade 3 headache that improves to grade ≤ 2 within 72 hours
     - grade 3 insomnia that improves to grade ≤ 2 within 72 hours
     - grade 3 fever that improves to grade ≤ 2 within 72 hours
     - grade 3 nausea, vomiting or diarrhea responding if managed with optimal medical support and resolves within 72 hours
     - laboratory parameters of grade ≥ 3, not considered clinically relevant **,** and improved to grade ≤ 2 within 72 hours
4. Hematologic DLTs:
   - Febrile neutropenia grade 3 or higher unless responding to antibiotic/anti-infective treatment within 48 hours
   - Grade 4 neutropenia lasting more than 5 days
   - Grade 4 thrombocytopenia lasting more than 7 days
   - Grade 3 thrombocytopenia with hemorrhage or required platelet transfusion
   - Grade 3 anemia with symptoms or required intervention (eg, transfusion)
   - Grade 4 anemia in the absence of detectable lymphoma as it may reflect a marrow toxic effect of AMG 562

Any adverse event, that meets the DLT definition, occurring outside the DLT evaluation period that is determined by the investigator to be possibly related to AMG 562, which is seen more frequently or is more severe than expected or is persistent despite appropriate management, can be determined to be a DLT upon unanimous decision by the DLRT after review of the adverse event and all available safety data.

An event should be considered related to treatment if, in the investigator's medical judgement, there is a reasonable possibility that the event may have been caused by AMG 562.

The dosing schedule is described by Part 1 Study Design and Schema and also in the protocol synopsis.

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

6.2.1.4.1 Infusion Interruptions/Delays/Withholding and Re-Start in Case of Technical/Logistical Issues

Events leading to infusion interruption or delay for technical/logistical reasons may include: technical problem with the infusion pump or the investigational product is incorrectly prepared or administered.

Infusion Interruptions due to Technical/Logistical Issues

The administration of AMG 562 should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible.

In case of infusion interruption, immediately consult with Amgen Medical Monitor to determine if

- AMG 562 stability is sufficient to administer the remaining infusion or
- a new infusion can be administered or
- the dose should be withheld

If the remaining infusion can be administered, no specific precautions have to be taken. If a new infusion can be administered, follow the procedures in the schedule of assessments (Table 8 through Table 11) for the day on which the original (interrupted) infusion was administered. Premedication as described in Section 6.3 for the first infusion of the treatment should be administered. If the infusion will need to be withheld, follow the instructions for re-start after interruptions due to adverse events described below for the next infusion.

Infusion Delay due to Technical/Logistical Issues

If the infusion delay was up to 72 hours, the dose can be administered without specific precautions. Procedures performed will follow the schedule of assessments for the treatment day on which the infusion was originally planned. The following infusion should then be administered after 7 (± 1) days; eg, if the Day 8 infusion needs to be

delayed for logistical issues, and could only be administered on Day 10, the next infusion should be administered on Day 17 (± 1 day) rather than the regular Day 15. The ± 1 day window is allowed until the original dosing schedule is met again (in the example above, the third infusion could be administered on Day 16, and the fourth infusion on Day 22, if preferred for logistical reasons).

If the delay of the next infusion was > 72 hours, the dose will need to be skipped and the instructions for re-start after interruptions due to adverse events described below should be followed.

6.2.1.4.2 Infusion Interruptions/Delays/Withholding and Re-Start due to Adverse Events

6.2.1.4.2.1 General Guidelines

Subjects should be assessed for toxicity before each infusion of AMG 562. The severity of the toxicity will be graded using the CTCAE version 4.0 (Appendix A), with the exception of CRS, which must be graded using the criteria referenced in the publication by Lee et al, 2014 (see Table 7) and TLS, which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008 (see Appendix K). Infusion modification and dose reduction due to a toxicity will be performed according to the instructions described below and outlined in Table 6 and Table 7.

Table 6. Infusion Interruptions/Delays/Withholding/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption/Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction				
Grade 1	n/a	Consider medication to control infusion reaction as deemed appropriate by the investigator according to local standard of care and institutional guidelines. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable	n/a	n/a
Grade 2	Immediate interruption/delay until event has improved to grade ≤ 1		• Re-start possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. • If the next infusion is delayed: – up to 72 hours: follow the schedule of assessments for the treatment day on which the infusion was originally planned. The following infusion should then be administered after 7 (± 1) days – > 72 hours: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: premedication and additional assessments as indicated in Section 6.2.1.4.2.4 above	If subject missed more than 2 consecutive doses

Page 1 of 5

Footnotes defined on last page of table

Table 6. Infusion Interruptions/Delays/Withholding/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Infusion-related Reaction (continued)				
Grade 3	Immediate interruption/ delay until event has improved to grade ≤ 1	Consider supportive therapy including steroids as clinically indicated. Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.	• As for grade 2 infusion-related reaction, with the exception of mandatory dose modification: reduce to next lower dose	If subject missed more than 2 consecutive doses If recurrent grade 3
Recurrent Grade 3 despite reduction of infusion rate & other measures	Immediate interruption	As for grade 3 infusion-related reaction	• n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 562 therapy
Grade 4	Immediate interruption	As for grade 3 infusion-related reaction	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 562 therapy
Cytokine Release Syndrome				
For Grading, Stopping and Re-challenge Rules please refer to Table 7.				

Footnotes defined on last page of table

Table 6. Infusion Interruptions/Delays/Withholding/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Any other adverse events including those not meeting DLT criteria				
≥ Grade 3	Interruption/ delay required if deemed intolerable by the subject and not responding to appropriate medical management until event has improved to grade ≤ 1	n/a	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. • If next infusion is delayed: – up to 72 hours: follow the schedule of assessments for the cycle day on which the infusion was originally planned. The following infusion should then be administered after 7 (± 1) days – > 72 hours: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: premedication and additional assessments as indicated in Section 6.2.1.4.2.4 above.	If subject missed more than 2 consecutive doses In case of any event at grade 4

Page 3 of 5

Footnotes defined on last page of table

Table 6. Infusion Interruptions/Delays/Withholding/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
CNS grade 3	Interrupt AMG 562 immediately	Perform investigations per local practice including neuro exam, cerebral MRI and CSF analysis Dexamethasone should be administered at a dose of 3 x 8 mg /d over 3 days with step-wise dose reduction over up to 4 days	• Re-start possible within 2 weeks but not earlier than 3 days after infusion was stopped if successfully managed and improvement to ≤ grade 1 in ≤ 7 days. • Hospitalization: 72 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • • Additional measures: premedication and additional assessments as indicated in Section 6.2.1.4.2.4 and Section 6.2.1.4.2.5 above.	In case CNS event needed more than 7 days after treatment interruption to resolve to grade ≤ 1
CNS grade 4*	Interrupt AMG 562 immediately	As for grade 3 CNS-related event	n/a	Permanently discontinue AMG 562 therapy
Seizure grade ≤ 2*	Interrupt AMG 562, administer corticosteroids and antiseizure medication per local practice	n/a	• Do not re-initiate AMG 562 until 7 days after the last seizure and after therapeutic levels of antiseizure medication are likely to have been achieved	Permanently discontinue if a 2nd seizure occurs with re-initiation of AMG 562
Seizure grade ≥ 3*	Interrupt AMG 562 immediately	Administer corticosteroids and antiseizure medication per local practice	n/a	Permanently discontinue AMG 562 therapy

Page 4 of 5

Footnotes defined on last page of table

Table 6. Infusion Interruptions/Delays/Withholding/Permanent Discontinuations and Management of Adverse Events Including Dose Reductions

	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Any Non-AMG 562 related events				
Grade 4	Interruption/ delay required if deemed intolerable by the subject and not responding to appropriate medical management until event has improved to grade ≤ 1, with exception of Grade 4 neutropenia or thrombocytopenia, follow re-start guidance as indicated.	n/a	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. • If next infusion is delayed: – up to 72 hours: follow the schedule of assessments for the cycle day on which the infusion was originally planned. The following infusion should then be administered after 7 (± 1) days – > 72 hours: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: resume at the same dose or reduce to next lower dose if clinically indicated • Additional measures: premedication and additional assessments as indicated in Section 6.2.1.4.2.4 above.	If subject missed more than 2 consecutive doses In case of reappearance of same event at grade 4
Hepatotoxicity				
For Stopping and Rechallenge Rules please refer to Section 6.4				

*** Obtain brain MRI and perform cerebro spinal fluid (CSF) analysis, if there are no contraindications**

6.2.1.4.2.2 Infusion Interruptions due to Adverse Events

Events occurring during the infusion and requiring treatment interruption will be managed by immediate infusion interruption. The site should record any unscheduled interruption of an infusion on the eCRF, and provide the start and stop date/time of the infusion.

Events requiring infusion interruption or permanent discontinuation are listed in Table 6.

6.2.1.4.2.3 Delay of Subsequent Infusion due to Adverse Events

Events occurring after the end of the infusion and requiring a delay of treatment will be managed by delay of the subsequent infusion. The site should record any delay of an infusion on the eCRF, and provide the start and stop date/time of the infusion.

Events requiring a delay of the subsequent infusion are listed in Table 6.

Note: For single subject cohorts, replace a subject if an infusion is delayed during the DLT evaluation period by > 7 days for a reason other than a DLT (ie, the subject will miss 1 out of the 4 planned doses and therefore is not evaluable for DLT).

For multiple subject cohorts, replace a subject if an infusion is delayed during the DLT evaluation period by > 14 days for a reason other than a DLT (ie, the subject will miss at least 2 consecutive doses out of the 4 planned doses and therefore is not evaluable for DLT).

After the end of the DLT period, subjects will not be replaced.

Infusion interruptions or delays for other reasons need to be discussed with the Amgen Medical Monitor.

6.2.1.4.2.4 Re-Start of Infusion

Re-starting treatment after an interruption/delay due to an adverse event or if the interruption/ delay was > 72 hours, regardless of the reason, should be performed under medical supervision. Premedication as described in Section 6.3 for the first infusion of the treatment should be considered prior to re-start. The following assessments should be performed as for Days 1, 2, and 3 of the treatment (see Schedule of Assessments, Table 8):

- vital signs, pulse oximetry,
- physical examination (including neurological examination, if applicable)
- weight

- ECOG
- safety Labs (hematology, chemistry, coagulation, urinalysis)

The subject should be hospitalized for at least 48 hours after re-start of the infusion.

6.2.1.4.2.5 Dose Adjustments and Re-Start at a Lower Dose Level

For adverse events for which restart of treatment is allowed according to the guidelines outlined in Table 6 and Table 7, treatment may be resumed at the same dose or a lower dose.

Re-start at a lower dose level:

In the following cases, the next infusion administered should be at the previous (lower) dose level:

- If the event occurred during the infusion and caused an interruption of the infusion for more than 72 hours and therefore the affected dose was withheld, or
- If the event started after the end of an infusion and administration of the next infusion had to be delayed for more than 72 hours due to the event.
- If grade 3 CRS, the next infusion should be restarted 1 dose level below the dose at which the event occurred. If this lower dose level is well tolerated (ie, absence of grade ≥ 2 CRS), then escalation to the subject's target dose level can occur for the next planned dose
- For specific events as outlined in Table 6.

In either case, re-escalation to the target dose can be considered for the next infusion if treatment at the lower dose has been well tolerated with no events requiring dose interruption or delay as described in Table 6 and Table 7. After the dose re-escalation, the following assessments should be performed as for Day 8 through Day 11 of the treatment per the Schedule of Assessments(with step-up dosing, Table 9):

- vital signs, pulse oximetry
- physical examination (including neurological examination, if applicable)
- safety labs (hematology, chemistry, coagulation, urinalysis)

The subject should be hospitalized for at least 48 hours after re-escalation.

In case an additional dose de-escalation is required, permanently discontinue treatment.

6.2.1.4.2.6 Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome is clinically defined and may have various manifestations. There are no established diagnostic criteria. Signs and symptoms of CRS may include:

- constitutional: fever, rigors, fatigue, malaise

- neurologic: headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure
- respiratory: dyspnea, tachypnea, hypoxemia
- cardiovascular: tachycardia, hypotension
- gastrointestinal: nausea, vomiting, transaminitis, hyperbilirubinemia
- hematology: bleeding, hypofibrinogenemia, elevated D-dimer
- skin: rash

Subjects may be at an increased risk for CRS during the first few days following the infusion of AMG 562. CRS may be life threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the treatment with AMG 562, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Grading and management of CRS should be performed according to the guidelines provided in Table 7 (based on the adopted grading system referenced in Lee et al, 2014).

After grade 2 or 3 CRS, the next scheduled infusion may be administered if all of the following criteria are met:

- The Amgen Medical Monitor must be consulted prior to re-starting treatment
- If CRS occurred during AMG 562 infusion, infusion has been interrupted for at least 72 hours

The event has resolved to grade ≤ 1 prior to re-starting treatment

Please also refer to the general guidance for re-start of infusion after interruptions/delay/withholding and dose modifications in Section 6.2.1.4.2.

For grade 3 and 4 CRS, please also see Section 6.2.1.3 for DLT considerations.

Table 7. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Interruption/ Delay/ Withholding	Minimum Expected Intervention	Restart Guidance	Permanent Discontinuation
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	n/a	Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever). Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is later.	n/a	n/a
2	Symptoms require and respond to moderate intervention • Oxygen requirement < 40%, OR • Hypotension responsive to fluids or low dose of 1 vasopressor, OR • Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Immediately interrupt/ delay AMG 562 until event improves to CRS grade ≤ 1.	Administer: • Symptomatic treatment (eg, paracetamol/ acetaminophen for fever) • Supplemental oxygen when oxygen saturation is < 90% on room air • Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. Investigators may also consider use of tocilizumab[c] as an additional therapy in this setting at a dose of 8 mg/kg IV as a single dose. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below.	• Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen medical monitor first. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. • If the next infusion is delayed: – up to 72 hours: follow the schedule of assessments for the treatment day on which the infusion was originally planned. The following infusion should then be administered after 7 (± 1) days – > 72 hours: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: 48 hours • Dose modification: reduce to next lower dose • Additional measures: premedication and additional assessments as indicated in Section 6.2.1.4.2.4 above	If there is no improvement to CRS ≤ grade 1 within 7 days. In case of 2 separate grade 2 or 3 CRS events.

Page 1 of 3

Footnotes defined on last page of this table

Table 7. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Interruption/ Delay/ Withholding	Minimum Expected Intervention	Restart Guidance	Permanent Discontinuation
3	Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40%, OR • Hypotension requiring high dose[b] or multiple vasopressors, OR • Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Immediately interrupt / delay AMG 562 until event improves to CRS grade ≤ 1.	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV or PO at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise. Additionally, tocilizumab[c] should be administered at a dose of 8 mg/kg IV as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	Re-start possible if successfully managed and improved to ≤ grade 1 within 7 days. • Consult with Amgen medical monitor first. • In case of infusion interruption, continue treatment with next scheduled infusion, do not resume prior infusion or administer delayed infusion. • If the next infusion is delayed: - up to 72 hours: follow the schedule of assessments for the treatment day on which the infusion was originally planned. The following infusion should then be administered after 7 (± 1) days - > 72 hours: skip the infusion and resume schedule of assessments for the next scheduled infusion • Hospitalization: at least 48 hours after CRS resolves to grade ≤ 2 • Dose modification: reduce to next lower dose • Additional measures: premedication and additional assessments as indicated in Section 6.2.1.4.2.4 above	If there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days. If CRS grade 3 occurs at the initial run in dose (ie, at MTD1), if applicable. In case of 2 separate grade 2 or 3 CRS events.

Page 2 of 3

Footnotes defined on last page of this table

Table 7. Grading and Management of Cytokine Release Syndrome

CRS Grade	Description of Severity[a]	Interruption/ Delay/ Withholding	Minimum Expected Intervention	Restart Guidance	Permanent Discontinuation
4	Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria		Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV or PO at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, tocilizumab[c] should be administered at a dose of 8 mg/kg IV as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	n/a	Immediately stop the infusion (if applicable) and permanently discontinue AMG 562 therapy

Page 3 of 3

CRS = Cytokine Release Syndrome, CTCAE = Common Terminology Criteria for Adverse Events, IV = Intravenous

[a] Revised grading system for cytokine release syndrome (Lee et al, 2014)

[b] High dose vasopressors (all doses are required for ≥3 hours): Norepinephrine monotherapy ≥ 20 µg/min; Dopamine monotherapy ≥ 10 µg/kg/min, Phenylephrine monotherapy ≥ 200 µg/min, Epinephrine monotherapy ≥ 10 µg/min; If on vasopressin, vasopressin + norepinephrine equivalent of ≥ 10 µg/min; If on combination vasopressors (not vasopressin), norepinephrine equivalent of ≥ 20 µg/min

[c] All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and 2 doses of tocilizumab per study subject.

6.2.1.4.3 Specific Guidance for Neurotoxicity

Neurotoxicity is a broad concept, including any adverse effect on the structure or function of the central and/or peripheral nervous system by a biological, chemical or physical agent. In this definition, neurotoxic effects may be permanent or reversible and result from direct or indirect actions on the nervous system (Erinoff, 'Interagency Committee on Neurotoxicology', 1995).

In case of grade 3 or grade 4 neurotoxicity events, perform investigations per local practice including neurological exam, cerebral MRI and CSF analysis after interruption of infusion.

Dexamethasone IV or PO should be administered at a dose of 3 x 8 mg /d over 3 days with step-wise dose reduction over up to 4 days. For seizures ≥ grade 2 administer corticosteroids and antiseizure medication per local practice.

Re-start of IP is possible within 2 weeks but not earlier than 3 days after infusion was stopped and if successfully managed with improvement to ≤ grade 1 in ≤ 7 days. Subjects will remain hospitalized for 72 hours following re-start of IP. Following grade 2 seizure, do not re-initiate AMG 562 until 7 days after the last seizure and after therapeutic levels of antiseizure medication are likely to have been achieved.

6.2.1.4.4 Permanent Discontinuation of AMG 562

AMG 562 treatment will be permanently discontinued in the event of:

- infusion-related reaction grade 4 (the infusion has to be stopped immediately, if applicable)
- recurrent grade 3 infusion-related reaction despite reduction of infusion rate & other symptomatic measures
- grade 4 CRS
- grade 2 or 3 CRS meeting any of the criteria listed below:
  - grade 2 or 3 CRS that does not improve to grade ≤ 1 within 7 days
  - grade 3 CRS that does not improve to grade ≤ 2 within 5 days
  - if a subject experiences 2 separate grade 2 or grade 3 CRS events regardless of dose
  - grade 3 CRS at the initial lower dose for treatment initiation (for cohorts with step-up dosing only)
- Occurrence of acute kidney injury considered related to AMG 562 by the investigator and meeting one or more of the following criteria:
  - Creatinine > 3x baseline or > 4.0 mg/dL and not recovered to CTCAE grade 1 or ≤ 0.3 mg/dL within 21 days
  - Hemodialysis required

- DLT (separate guidance for CRS, IRR and Neurotoxicity) or other unmanageable toxicity unless a subject has a clear clinical benefit from treatment, the toxicity has resolved to grade ≤ 1 or baseline and after consultation with the sponsor
- in case of grade 4 non-hematologic adverse event
- grade 3 neurotoxicity needing more than 7 days after treatment interruption to resolve to grade ≤1
- Grade 4 neurotoxicity
- Grade ≥ 3 seizure
- In case of occurrence of more than one seizure of grade ≤ 2
- treatment interruption: if the subject misses at least 2 consecutive doses due to serious adverse events/adverse events
- possible DILI requiring permanent withholding as per Section 6.4
- subjects who require more than 1 dose reduction
- clinically relevant disease progression
- relapse of disease subsequent to response on protocol treatment
- occurrence or progression of a medical condition which in the opinion of the investigator should preclude further participation of the subject in the study
- administration of relevant non-permitted concomitant medications
- requirement for alternative therapy
- subject's request
- subject or investigator not compliant with the study protocol

For grading of events, refer to Section 9.2.2.1.

Females who become pregnant while on study through 120 days after receiving the last dose of study drug will not receive subsequent scheduled doses and will be followed for safety until the EOS visit.

Males with pregnant partners or whose partners become pregnant while the subject is on study through 180 days after receiving the last dose of study drug must practice sexual abstinence or use a condom while on study through 180 days after receiving the last dose of study drug.

All reasons for treatment discontinuation should be clearly and comprehensively documented in the eCRF. If a subject has not continued to present for study visits, the investigator should determine the reason and circumstances as completely and accurately as possible.

In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the EOT.

6.3 Other Protocol-required Therapies

All other protocol-required therapies including glucocorticoids that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Premedication for Cycle 1: an 8 mg dose of IV or PO dexamethasone approximately 1 hour prior to the start of the AMG 562 infusion is mandatory:

- Prior to each infusion in Cycle 1 8 mg dexamethasone IV or PO as premedication

Premedication for Cycle 2 and beyond:

- Pre medication with 8 mg IV or PO dexamethasone for each subsequent cycle will be required for any subject who experienced grade ≥ 2 neurotoxicity or grade ≥ 2 CRS in the preceding cycle
- If CRS and neurotoxicity of grade 2 or higher did not occur in the prior cycle(s), premedication with dexamethasone can be reduced to 4 mg. If subjects tolerate AMG 562 well with reduced dose dexamethasone, premedication with dexamethasone can be discontinued for the next cycle in consultation with Amgen Medial Monitor.

No additional premedication is permitted on the trial.. If the evaluation of available safety and laboratory data suggests that adjustment to the dexamentasone schedule are required or additional premedication is necessary the DLRT can recommend to adjust the current schedule and/or add additional premedication, eg, antihistamines and H2 blockers to the premedication regimen. In this case all future cohorts will receive this additional premedication. All subjects will be pre-treated unless a contraindication for this premedication exists.

Premedication as described above for the first infusion also has to be administered after treatment interruptions / delays as described in Section 6.2.1.4.

For administration of dexamethasone and tocilizumab after occurrence of CRS, follow guidance in Table 7. All sites will ensure that CRS rescue medications are available on-site, including corticosteroids and 2 doses of tocilizumab per study subject.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

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

6.4.1 Criteria for Permanent Withholding of AMG 562 due to Potential Hepatotoxicity

AMG 562 should be permanently withheld and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible DILI, if ALL of the criteria below are met:

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

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

AND

- TBIL > 2 x ULN or INR > 1.5

AND

- No other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or elevated TBIL values include, but are not limited to:
  - hepatobilliary tract disease
  - viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
  - right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
  - exposure to hepatotoxic agents/drugs including herbal and dietary supplements, plants, and mushrooms,
  - heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - alpha-one antitrypsin deficiency
  - alcoholic hepatitis
  - autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - nonalcoholic fatty liver disease including steatohepatitis (NASH)
  - non-hepatic causes (eg, rhabdomyolysis, hemolysis)

6.4.2 Criteria for Conditional Withholding of AMG 562 due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of AMG 562 outlined above and have no underlying liver disease and eligibility criteria requiring normal transaminases and TBIL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol-required therapies:

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

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

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

AMG 562 should be withheld pending investigation into alternative causes of the laboratory elevations. If AMG 562 is withheld, the subject should be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for the elevated liver enzymes (ALT, AST, ALP) and/or elevated TBIL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

Discontinuation of the product should be considered and the decision to rechallenge should be discussed with the Amgen Medical Monitor before reinitiating treatment with investigational product.

6.4.3 Criteria for Rechallenge of AMG 562 After Potential Hepatotoxicity

If signs or symptoms recur with rechallenge, then AMG 562 should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1.4) should not be rechallenged.

6.5 Concomitant Therapy

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

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

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

6.5.1 Supportive Care

Subjects should receive supportive care according to local guidelines for blood product support, antibiotics, antivirals, analgesics, etc.

Throughout the study, subjects should be encouraged to remain well hydrated throughout the treatment period.

Please refer to Sections 6.2.1.4.2.2 and 6.2.1.4.2.6 for management of CRS and infusion related reaction.

Oxygen administration as supportive measure is permitted during study treatment.

6.5.2 Growth Factors

The use of growth factors such as erythropoiesis-stimulating proteins as well as G-CSF will be allowed during therapy. However, growth factors are not allowed at inclusion (within 7 days of applicable screening assessment) and should be avoided, if subject`s condition allows, in the first four weeks of treatment for better assessment of safety parameters.

6.5.3 Infections

Prophylactic antibiotics, antifungal and antivirals are allowed and should be given as per institutional standards and as per recommendation below. Subjects who experience neutropenia for 7 days or longer are at a high risk for infectious complications. Therefore if ANC < 0.5 x 10^9, all patients should have anti-bacterial and anti-fungal prophylaxis started using agents according to institutional standard. These subjects should be monitored for early signs of breakthrough infections after the initiation of antibacterial therapy to prompt additional evaluation and possible therapy modification.

Subjects with evidence of existing infection after the start of AMG 562 treatment should be closely monitored while being treated with AMG 562. Subjects with active systemic infections requiring IV antibiotics, antivirals, or antifungals should not be dosed with AMG 562 until infection has resolved and if being treated with an IV anti-infectious therapy, the course of such therapy should have been completed.

Management should be tailored to the appropriate prophylaxis and/or treatment for the underlying infection according to the local standard of care and institutional guidelines.

6.6 Medical Devices

Investigational product must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment. Investigational product infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines that are compatible with the investigational product. Additional medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not provided or reimbursed by Amgen (except, if required by local regulation). The investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

6.7 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

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

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

6.8 Excluded Treatments, Medical Device Use, and/or Procedures During Study Period

The following treatments and/or procedures are excluded during the treatment period of the study (until SFU):

- any antitumor therapy other than AMG 562, such as:
  - cytotoxic and/or cytostatic drugs
  - radiation therapy (with the exception of radiotherapy for palliative care such as bone pain; this is only permitted after discussion with Amgen Medical Monitor)
  - immunotherapy
- any other immunosuppressive therapies (except for the management of acute, treatment–related toxicities such as transient – ie, for up to 2 weeks - use of corticosteroids and tocilizumab)
  - high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent) is only allowed for up to 7 days
- any other investigational agent
- treatment with growth factors, IV antibiotics, antivirals, or antifungals during DLT window unless discussed with the Amgen Medical Monitor
- treatment with medications known to cause QTc interval prolongation unless approved by the Amgen Medical Monitor (see Appendix E)
- treatment with medications that are CYP450 substrates with a narrow therapeutic index in cycles 1 and 2 unless approved by the Amgen Medical Monitor (see Appendix G for examples). In case use of these substrates is approved, appropriate monitoring for potentially increased toxicity should be implemented.
- any major surgery

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 8. Schedule of Assessments for Screening and Treatment Cycle 1

	SCR	Treatment Period (Cycle 1)																																																						
Cycle Day	-21 to -1	1[b]											2	3	4	8[a]											9	10	11	15[a]										16	17	18	20	22[a]										23	24	25
			Relative to start of infusion														Relative to start of infusion														Relative to start of infusion														Relative to start of infusion											
Hours		Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48		Predose	0	[redacted]	2	4	6	8	12	16	20	24	48			Predose	0	[redacted]	2	4	6	8	12	16	20	24	48	
GENERAL AND SAFETY ASSESSMENTS																																																								
ICF	X																																																							
Hospitalization[c]				------------------------------------->													------------------------------------->														------------------------------------->															------------------------------------->										
Demographics	X																																																								
Height	X																																																							
Medical history	X																																																							
Con meds	X	X		<------------------------------ continually throughout treatment ------------------------------>																																																
SAE review	X	X		<------------------------------ continually throughout treatment ------------------------------>																																																
AE/DRE review			X	<------------------------------ continually throughout treatment ------------------------------>																																																
Physical exam	X	X											X	X	X	X											X	X	X	X										X	X	X		X												X
Neurological exam	X	X						x[t]					x[t]	x[t]	x[t]	X								x[t]			x[t]	x[t]	x[t]	X					x[t]					x[t]	x[t]	x[t]		X										x[t]	x[t]	x[t]
ECOG	X	X																																																						X
Weight	X	X																																																						
Vitals/pulse ox[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
ECG triplicate[d]	X	X		X				X		X			X	X	X	X		X										X		X		X									X			X		X			X		X			X	X	X
INVESTIGATIONAL PRODUCT DOSING																																																							
AMG 562 IV[b]			X														X														X														X											
Premedication[e]		X														X														X														X												

Page 1 of 4

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Table 8. Schedule of Assessments for Screening and Treatment Cycle 1

	SCR	Treatment Period (Cycle 1)													
Cycle Day	-21 to -1	1[b]											2	3	4
			Relative to start of infusion												
Hours		Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72
LABORATORY ASSESSMENTS															
Pregnancy test[f]	X	X													
Coagulation[q]	X	X							X				X	X	
Hem, chem[q]	X	X							X				X	X	
Ferritin[g]		X	<-- at onset of CRS, and daily until values are back to baseline/event is resolved ------------------------>												
CSF analysis [m, p]	Collect if grade ≥3 neurologic event or seizure grade ≤ 2[p]														
C-reactive protein		X											X	X	
Hepatitis serology	X														
Urinalysis	X	X												X	
Ig: IgA, IgM, IgG	X	X													
Anti-AMG 562-Ab		X[h]													
BIOMARKER ASSESSMENTS															

	Treatment Period (Cycle 1)													
Cycle Day	8[a]											9	10	11
		Relative to start of infusion												
Hours	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	
LABORATORY ASSESSMENTS														
Pregnancy test[f]														
Coagulation[q]	X											X	X	
Hem, chem[q]	X											X	X	
Ferritin[g]														
CSF analysis [m, p]														
C-reactive protein	X											X	X	
Hepatitis serology														
Urinalysis	X												X	
Ig: IgA, IgM, IgG														
Anti-AMG 562-Ab														
BIOMARKER ASSESSMENTS														

	Treatment Period (Cycle 1)													
Cycle Day	15[a]										16	17	18	20
		Relative to start of infusion												
Hours	Predose	0	[redacted]	2	4	6	8	12	16	20	24	48		
LABORATORY ASSESSMENTS														
Pregnancy test[f]														
Coagulation[q]	X										X	X		
Hem, chem[q]	X										X	X		
Ferritin[g]														
CSF analysis [m, p]														
C-reactive protein	X										X	X		
Hepatitis serology														
Urinalysis	X											X		
Ig: IgA, IgM, IgG														
Anti-AMG 562-Ab	X													
BIOMARKER ASSESSMENTS														

	Treatment Period (Cycle 1)												
Cycle Day	22[a]										23	24	25
		Relative to start of infusion											
Hours	Predose	0	[redacted]	2	4	6	8	12	16	20	24	48	
LABORATORY ASSESSMENTS													
Pregnancy test[f]													
Coagulation[q]	X										X	X	X
Hem, chem[q]	X										X	X	X
Ferritin[g]													
CSF analysis [m, p]													
C-reactive protein	X												
Hepatitis serology													
Urinalysis	X											X	X
Ig: IgA, IgM, IgG													X
Anti-AMG 562-Ab													
BIOMARKER ASSESSMENTS													

[redacted]

Page 2 of 4

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Table 8. Schedule of Assessments for Screening and Treatment Cycle 1

	SCR	Treatment Period (Cycle 1)																											
Cycle Day	-21 to -1	1[b]											2	3	4	8[a]											9	10	11
Hours		Predose	Relative to start of infusion: 0	[redacted]	2	3	4	6	8	12	16	20	24	48	72	Predose	Relative to start of infusion: 0	[redacted]	2	3	4	6	8	12	16	20	24	48	
BIOMARKER ASSESSMENTS (continued)																													
[redacted]																													
PK ASSESSMENTS																													
AMG 562 PK[n, r]		X*		X				X		X			X	X	X	X*		X											

	Treatment Period (Cycle 1)																										
Cycle Day	15[a]										16	17	18	20	22[a]										23	24	25
Hours	Predose	Relative to start of infusion: 0	[redacted]	2	4	6	8	12	16	20	24	48			Predose	Relative to start of infusion: 0	[redacted]	2	4	6	8	12	16	20	24	48	
BIOMARKER ASSESSMENTS (continued)																											
[redacted]																											
PK ASSESSMENTS																											
AMG 562 PK[n, r]	X*		X												X*		X			X		X			X	X	X

Page 3 of 4

Footnotes defined on last page of this table

Table 8. Schedule of Assessments for Screening and Treatment Cycle 1

	SCR		Treatment Period (Cycle 1)
Cycle Day	-21 to -1		1[b] 2 3 4 | 8[a] 9 10 11 | 15[a] 16 17 18 20 | 22[a] 23 24 25
Hours		Predose	Relative to start of infusion: 0 [redacted] 2 3 4 6 8 12 16 20 24 48 72 | Predose 0 [redacted] 2 3 4 6 8 12 16 20 24 48 | Predose 0 [redacted] 2 4 6 8 12 16 20 24 48 | Predose 0 [redacted] 2 4 6 8 12 16 20 24 48
DISEASE ASSESSMENTS			
BM aspirate/ biopsy[j]	X		<---------- Optional at week 5 (C2D1) ---------->
COO/FISH lymph node biopsy[k]	X		
LN biopsy for DLBCL following prior CD19-targeted treatment failure[l]	X		<---------- Optional at relapse, post AMG 562 treatment, in responders ---------->
RADIOGRAPHIC ASSESSMENTS			
MRI[s]/PET/CT[o]	x		

Ab = antibody, AE = adverse event; BM = bone marrow, chem = chemistry, con meds = concomitant medications, COO = cell of origin, CR = complete response, CRS = Cytokine Release Syndrome, ctDNA = circulating tumor DNA, CT = computed tomography, demo = demographics, DRE = disease-related event; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, Expl = exploratory, FISH = fluorescent insitu hybridization, hem = hematology, ICF = informed consent form, Ig = immunoglobulins, LN= lymph node, LTFU = long-term follow-up, med hist = medical history, MRD = minimal residual disease, MRI = magnetic resonance imaging, neuro = neurological, NGS = next generation sequencing, ox = oximetry, PB = peripheral blood, PD = progressive disease, periph. = peripheral, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, SCR = screening, SFU = safety follow-up,

[a] The Dose Level Review Team (DLRT) may recomend to change timing of D8/D15/D22 within a window of ± 1 day. In this case, timing of the following visits would be adjusted accordingly.

[b] In case of step-dosing, the subsequent treatments will be at weekly intervals after the target dose is administered.

[c] See Section 6.2.1.1 for details on hospitalization requirements.

[d] ECGs and vital signs should be performed prior to any invasive procedures. ECGs are only required in treatment cycle 1 and 2. In case of intra-subject dose escalation: conduct ECGs as in cycle 1 during the first cycle after dose escalation.

[e] For premedication details see Section 6.3.
[f] Serum pregnancy test required at screening. For later time points, urine pregnancy test is allowed. In case of a positive result, serum pregnancy test should be repeated. Pregnancy tests will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[g] Ferritin assessment to be performed at onset of CRS, and daily until values are back to baseline/event is resolved.
[h] Predose anti-AMG 562 antibody sample in every 2nd cycle after cycle 1 (C1D1, C1D15, C3D1, C5D1, ..).

[o] PET/CT will be performed at screening, week 5, week 15, week 25 and and at end of treatment if end of treatment is at week 35 or beyond. Clinical tumor assessments will be performed at screening, week 5, week 15, week 25 and at end of treatment if end of treatment is at week 35 or beyond. Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment. If subject discontinues study treatment for any reason, including toxicity or clinical evidence of disease progression, PET/CT should be conducted 14 (+ 3) days following the last dose of AMG 562.
[p] In case of seizure of any grade perform brain MRI and cerebro spinal fluid (CSF) analysis, if there are no contraindications.
[q] As indicated in Section 7.3.10, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and D-dimer
[r] PK samples should be collected at the exact nominal time point specified; all times are relative to the start of infusion. The [redacted] hour sample is the same as the end of infusion and should be collected as close as possible to the end of infusion of AMG 562. If unable to collect a PK sample at the specified nominal time point, then collect the sample as close as possible and record the actual collection time. The exact date and time of IP administration and PK sample collection should be documented. Additional PK samples may be collected per the discretion of the PI as clinically indicated.
[s] MRI of the brain to be performed at screening. To be repeated during treatment in case of seizure
[t] Limited neurological examinations to be performed at these timepoints when hospitalized or in clinic as described in Section 7.3.9.2. Writing test to be performed on mornings and evenings on C1D1, C1D2 and after step-up dose treatment initiation

Table 9. Schedule of Assessments for Screening and Treatment Cycle 1 With 24 hour Step-up Dosing Intervals

Treatment Period (Cycle 1)

Cycle Day	SCR -21 to -1	1[b]											2	3	4	5
Hours		Predose	Relative to start of infusion: 0		2	3	4	6	8	12	16	20	24	48	72	
GENERAL AND SAFETY ASSESSMENTS																
ICF	X															
Hospitalization[c]			------------------------------------->													
Demo/med hist /height	X															
Con meds	X	X	<--													
SAE review	X	X	<--													
AE/DRE review			X	<---												
Physical exam	X	X											X	X	X	
Neurological exam	X	X						x[t]					x[t]	x[t]	x[t]	
ECOG	X	X														
Weight	X	X														
Vitals/pulse ox[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
ECG triplicate[d]	X	X		X				X			X			X	X	

Cycle Day	8[a]											9	10	11
Hours	Predose	Relative to start of infusion: 0	[redacted]	2	3	4	6	8	12	16	20	24	48	
GENERAL AND SAFETY ASSESSMENTS														
ICF														
Hospitalization[c]		------------------------------------->												
Demo/med hist /height														
Con meds	continually throughout treatment													
SAE review	continually throughout treatment													
AE/DRE review	continually throughout treatment													
Physical exam	X											X	X	X
Neurological exam	X								x[t]			x[t]	x[t]	x[t]
ECOG														
Weight														
Vitals/pulse ox[d]	X		X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate[d]	X		X										X	

Cycle Day	15[a]											16	17	18	20
Hours	Predose	Relative to start of infusion: 0	[redacted]	2	4	6	8	12	16	20	24	48		
GENERAL AND SAFETY ASSESSMENTS														
ICF														
Hospitalization[c]		------------------------------------->												
Demo/med hist /height														
Con meds	--													
SAE review	--													
AE/DRE review	--													
Physical exam	X										X	X	X	
Neurological exam	X					x[t]					x[t]	x[t]	x[t]	
ECOG														
Weight														
Vitals/pulse ox[d]	X		X	X	X	X	X	X	X	X	X	X	X	
ECG triplicate[d]	X		X									X		

Cycle Day	22[a]											23	24	25
Hours	Predose	Relative to start of infusion: 0	[redacted]	2	4	6	8	12	16	20	24	48	
GENERAL AND SAFETY ASSESSMENTS													
ICF													
Hospitalization[c]		------------------------------------->											
Demo/med hist /height													
Con meds	-->												
SAE review	-->												
AE/DRE review	-->												
Physical exam	X												X
Neurological exam	X										x[t]	x[t]	x[t]
ECOG													
Weight													
Vitals/pulse ox[d]	X		X	X	X	X	X	X	X	X	X	X	X
ECG triplicate[d]	X		X			X		X			X	X	X

Page 1 of 4

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Table 9. Schedule of Assessments for Screening and Treatment Cycle 1 With 24 hour Step-up dosing Intervals

	SCR		Treatment Period (Cycle 1)																											
Cycle Day	-21 to -1		1[b]										2	3	4		8[a]											9	10	11
			Relative to start of infusion															Relative to start of infusion												
Hours		Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72		Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	
INVESTIGATIONAL PRODUCT DOSING																														
AMG 562 IV[b]			X										X					X												
Premedication[e]		X															X													
LABORATORY ASSESSMENTS																														
Pregnancy	X	X																												
Coagulation[q]	X	X							X				X	X			X							X				X	X	
Hem, chem[q]	X	X							X				X	X			X							X				X	X	
Ferritin[g]		X	<-- at onset of CRS, and daily until values are back to baseline/event is resolved ------------------------>																											
CSF analysis[m, p]			Collect if grade ≥3 neurologic event or seizure grade ≤ 2[p]																											
C-reactive protein		X											X	X	X		X											X	X	
Hepatitis serology	X																													
Urinalysis	X	X												X			X												X	
Ig: IgA, IgM, IgG	X	X																												
Anti-AMG 562-Ab		X[h]																												

	Treatment Period (Cycle 1)																										
Cycle Day		15[a]									16	17	18	20		22[a]									23	24	25
		Relative to start of infusion														Relative to start of infusion											
Hours	Predose	0	[redacted]	2	4	6	8	12	16	20	24	48			Predose	0	[redacted]	2	4	6	8	12	16	20	24	48	
INVESTIGATIONAL PRODUCT DOSING																											
AMG 562 IV[b]		X														X											
Premedication[e]	X														X												
LABORATORY ASSESSMENTS																											
Pregnancy																											
Coagulation[q]	X										X	X			X										X	X	
Hem, chem[q]	X										X	X			X										X	X	
Ferritin[g]																											
CSF analysis[m, p]																											
C-reactive protein	X										X	X			X												
Hepatitis serology																											
Urinalysis	X											X			X											X	
Ig: IgA, IgM, IgG																											
Anti-AMG 562-Ab	X																										

Page 2 of 4

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Table 9. Schedule of Assessments for Screening and Treatment Cycle 1 With 24 hour Step-up dosing Intervals

	SCR	Treatment Period (Cycle 1)																								
Cycle Day	-21 to -1	1[b]			2	3	4	8[a]			9	10	11	15[a]			16	17	18	20	22[a]			23	24	25
Hours		Predose	0	2	3	4	6	8	12	16	20	24	48	72	Predose	0	2	3	4	6	8	12	16	20	24	48
		Predose	0	2	4	6	8	12	16	20	24	48			Predose	0	2	4	6	8	12	16	20	24	48	
BIOMARKER ASSESSMENTS																										
[redacted]																										

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Table 9. Schedule of Assessments for Screening and Treatment Cycle 1 With 24 hour Step-up dosing Intervals

	SCR	Treatment Period (Cycle 1)																														
Cycle Day	-21 to -1	1[b]									2	3	4	8[a]									9	10	11	15[a]						
Hours		Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	Predose	0	[redacted]	2	4	6	8	12	16	20	24	48
PK ASSESSMENTS																																
AMG 562 PK[n, r]		X*		X*				X		X			X	X	X	X*		X										X*		X									
DISEASE ASSESSMENTS																																
BM aspirate/ biopsy[j]	X	<---------- Optional at week 5 (C2D1) ---------->																														
COO/FISH Lymph node biopsy[k]	X																															
LN biopsy for DLBCL following prior CD19-targeted treatment failure[s]	X	<---------- Optional at relapse, post AMG 562 treatment, in responders ---------->																														
RADIOGRAPHIC ASSESSMENTS																																
PET/CT[o]	x																															

Ab = antibody, AE = adverse event, BM = bone marrow, chem = chemistry; con meds = concomitant medications, CR = complete response, CRS = Cytokine Release Syndrome, ctDNA = circulating tumor DNA, CT = computed tomography, demo = demographics, DRE = disease-related event, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, Expl = exploratory, hem = hematology, ICF = informed consent form, Ig = immunoglobulins, LN= lymph node, LTFU = long-term follow-up, med hist = medical history, MRD = minimal residual disease, MRI = magnetic resonance imaging, neuro = neurological, NGS = next generation sequencing, ox = oximetry, PB = peripheral blood, PD = progressive disease, periph = peripheral, PET = positron emission tomography, PG = pharmacogenomics, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, SCR = screening, SFU = safety follow-up,

[a] The Dose Level Review Team (DLRT) may recommend to change timing of D8/D15/D22 within a window of ± 1 day. In this case, timing of the following visits would be adjusted accordingly. The DLRT may also recomend to move the dose step to D5. In this case, the following infusions would be administered on D12 and D19 (and not on D15 and D22), and the following cycle days would move in accordingly.
[b] In case of step-dosing, the subsequent treatments will be at weekly intervals after the target dose is administered.
[c] See Section 6.2.1.1 for details on hospitalization requirements
[d] ECGs and vital signs should be performed prior to any invasive procedures. ECGs are only required in treatment cycle 1 and 2. In case of intra-subject dose escalation: conduct ECGs as in cycle 1 during the first cycle after dose escalation.
[e] For premedication details see Section 6.3.
[f] Serum pregnancy test required at screening. For later time points, urine pregnancy test is allowed. In case of a positive result, serum pregnancy test should be repeated. Pregnancy tests will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[g] Ferritin assessment to be performed at onset of CRS, and daily until values are back to baseline/event is resolved
[h] Predose anti-AMG 562 antibody sample in every 2nd cycle after cycle 1 (C1D1, C1D15, C3D1, C5D1, ..).

[redacted]

[o] PET/CT will be performed at screening, week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond. Clinical tumor assessments will be performed at screening, week 5, week 15, week 25 and at end of treatment if end of treatment is at week 35 or beyond. Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment. If subject discontinues study treatment for any reason, including toxicity or clinical evidence of disease progression, PET/CT should be conducted 14 (+ 3) days following the last dose of AMG 562.
[p] In case of seizure of any grade perform brain MRI and cerebro spinal fluid (CSF) analysis, if there are no contraindications.
[q] As indicated in Section 7.3.10, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and D-dimer
[r] PK samples should be collected at the exact nominal time point specified; all times are relative to the start of infusion. The [redacted] hour sample is the same as the end of infusion and should be collected as close as possible to the end of infusion of AMG 562. For step dosing, intermediate doses will only require PK collection at predose and [redacted] hour (EOI). PK samples should be collected at the following time points after administration of the first target dose: predose, [redacted] (EOI), 6, 12, 24, 48, 72 hr relative to the start of infusion at the target dose.
[s] For DLBCL subjects who failed prior CD-19 therapy; a LN biopsy at screening is (mandatory) to test for CD19 expression unless no lesion is accessible or the investigator deems the risk of the biopsy too high. For patients responding to AMG 562 treatment an optional LN biopsy at relapse, post AMG 562 treatment in responders may be collected.
[t] Limited neurological examinations to be performed at these timepoints when hospitalized or in clinic as described in Section 7.3.9.2. Writing test to be performed on mornings and evenings on C1D1, C1D2 and after step-up dose treatment initiation

Table 10. Schedule of Assessments for Treatment Cycle 2

	Treatment Period (Cycle 2)																																																					
Cycle Day	1[b]											2	3	4	8[a]											9	10	11	15[a]										16	17	18	22[a]										23	24	25
Hours			Relative to start of infusion													Relative to start of infusion														Relative to start of infusion													Relative to start of infusion											
	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48		Predose	0	[redacted]	2	4	6	8	12	16	20	24	48		Predose	0	[redacted]	2	4	6	8	12	16	20	24	48	
GENERAL AND SAFETY ASSESSMENTS																																																						
Con meds	X		<--- continually throughout treatment --->																																																
SAE review	X		<--- continually throughout treatment --->																																																
AE/DRE review	X	X	<--- continually throughout treatment --->																																																
Hospitalization[c]			-------------->													-------------->														----------->													----------->											
Physical exam	X											X	X		X											X			X										X			X											
Neurological exam	X		<-- to be performed prior to discharge from clinic from cycle 2 and beyond --------------------------------------->																																																
ECOG	X																																																				
Weight	X																																																				
Vitals, pulse ox[d]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X		X
ECG triplicate[d]	X		X												X		X												X		X											X		X									
INVESTIGATIONAL PRODUCT DOSING																																																						
AMG 562 IV[b]		X														X														X													X										
Premedication[e]	X														X														X													X											

Page 1 of 3

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Table 10. Schedule of Assessments for Treatment Cycle 2

	Treatment Period (Cycle 2)																																																					
Cycle Day	1[b]											2	3	4	8[a]											9	10	11	15[a]										16	17	18	22[a]										23	24	25
Hours	Predose	Relative to start of infusion													Predose	Relative to start of infusion													Predose	Relative to start of infusion												Predose	Relative to start of infusion											
		0	[redacted]	2	3	4	6	8	12	16	20	24	48	72		0	[redacted]	2	3	4	6	8	12	16	20	24	48			0	[redacted]	2	4	6	8	12	16	20	24	48			0	[redacted]	2	4	6	8	12	16	20	24	48	
LABORATORY ASSESSMENTS																																																						
Pregnancy test[f]	X																																																					
Coagulation[p]	X							X				X	X		X											X			X										X			X										X		
Hem, chem[p]	X							X				X	X		X											X			X										X			X										X		
Ferritin[g]		<-- at onset of CRS, and daily until values are back to baseline/event is resolved ------------------------>																																																				
CSF analysis[l, o]		Collect if grade ≥3 neurologic event or seizure grade ≤ 2[o]																																																				
Urinalysis	X														X														X													X												
Ig: IgA, IgM, IgG	X																																																					
BIOMARKER ASSESSMENTS																																																						

[redacted]

Page 2 of 3

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Table 10. Schedule of Assessments for Treatment Cycle 2

	Treatment Period (Cycle 2)																																																					
Cycle Day	1[b]											2	3	4	8[a]											9	10	11	15[a]										16	17	18	22[a]										23	24	25
Hours		Relative to start of infusion														Relative to start of infusion														Relative to start of infusion													Relative to start of infusion											
	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48		Predose	0	[redacted]	2	4	6	8	12	16	20	24	48		Predose	0	[redacted]	2	4	6	8	12	16	20	24	48	
BIOMARKER ASSESSMENTS (Continued)																																																						
[redacted]																																																						
PK ASSESSMENTS																																																						
AMG 562 PK[m, r]	X*		X*												X*		X												X*		X											X*		X										
DISEASE ASSESSMENTS and RADIOGRAPHIC ASSESSMENTS																																																						
PET/CT[q]	X																																																					
BM aspirate/ biopsy[i]		<------------------ Optional at week 5 (C2D1) ---------------->																																																			

Page 3 of 3

Ab = antibody, AE = adverse event, BM = bone marrow, chem = chemistry; con meds = concomitant medications, CR = complete response, CRS = Cytokine Release Syndrome, ctDNA = circulating tumor DNA, CT = computed tomography, demo = demographics, DRE = disease-related event, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, Expl = exploratory, hem = hematology, Ig = immunoglobulins LTFU = long-term follow-up, MRD = minimal residual disease, MRI = magnetic resonance imaging, NGS = next generation frequencing, ox = oximetry, PB = peripheral blood, PD = progressive disease, periph = peripheral, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, SFU = safety follow-up

[a] The Dose Level Review Team may decide to change timing of D8/D15/D22 within a window of ± 1 day. In this case, timing of the following visits would be adjusted accordingly.

[b] In case of step-dosing, the subsequent treatments will be at weekly intervals after the target dose is administered.

[c] See Section 6.2.1.1 for details on hospitalization requirements
[d] ECGs and vital signs should be performed prior to any invasive procedures. ECGs are only required in treatment cycle 1 and 2. In case of intra-subject dose escalation: conduct ECGs as in cycle 1 during the first cycle after dose escalation. Vital Signs at hour 4 and beyond after each IP administration from cycle 2 will be performed if patient is hospitalized.
[e] For premedication details see Section 6.3.
[f] Serum pregnancy test required at screening. For later time points, urine pregnancy test is allowed, in case of a positive result, serum pregnancy test should be repeated. Pregnancy tests will be performed for all females unless surgically sterile or > 2 years postmenopausal.
[g] Ferritin assessment to be performed at onset of CRS, and daily until values are back to baseline/event is resolved.

[o] In case of seizure of any grade perform brain MRI and cerebro spinal fluid (CSF) analysis, if there are no contraindications.
[p] As indicated in Section 7.3.10, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and D-dimer
[q] PET/CT will be performed at screening, week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond. Clinical tumor assessments will be performed at screening, week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond. Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment. If subject discontinues study treatment for any reason, including toxicity or clinical evidence of disease progression, PET/CT should be conducted 14 (+ 3) days following the last dose of AMG 562.
[r] PK samples should be collected at the exact nominal time point specified; all times are relative to the start of infusion. The [redacted] hour sample is the same as the end of infusion and should be collected as close as possible to the end of infusion of AMG 562. If unable to collect a PK sample at the specified nominal time point, then collect the sample as close as possible and record the actual collection time. The exact date and time of IP administration and PK sample collection should be documented. Additional PK samples may be collected per the discretion of the PI as clinically indicated.

Table 11. Schedule of Assessments for Treatment Cycle 3 and Following to End of Study

	Treatment Period (Cycle 3 and following)																																												EoT	SFU	LTFU[c]
Cycle Day	1[b]											2	3	4	8[a]							9	10	11	15[a]						16	17	18	22[a]						23	24	25					Up to 2 yrs after 1st IP dose
Hours	Predose	Relative to start of infusion													Predose	Relative to start of infusion									Predose	Relative to start of infusion								Predose	Relative to start of infusion												
		0	[redacted]	2	3	4	6	8	12	16	20	24	48	72		0	2	4	6	8	12	24	48			0	4	6	8	12	24	48			0	4	6	8	12	24	48						
GENERAL AND SAFETY ASSESSMENTS																																															
Hospitalization[d]			-------------->													------->										--->									---->												
Con meds	X		<------ continually throughout treatment ------>																																												
Subsequent anti-lymphoma treatment																																															X
SAE review	X		<------ continually throughout treatment ------>																																												X[e]
AE/DRE review	X	X	<------ continually throughout treatment ------>																																												
Physical exam	X																																												X	X	
Neurological exam	X																																												X		
ECOG	X																																												X	X	
Weight	X																																												X	X	
Vitals, pulse ox[f]	X		X	X		X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	X			X	X	
ECG triplicate[f]																																													X	X	

Page 1 of 4

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Table 11. Schedule of Assessments for Treatment Cycle 3 and Following to End of Study

	Treatment Period (Cycle 3 and following)																																												EoT	SFU	LTFU[c]
Cycle Day	1[b]										2	3	4	8[a]							9	10	11	15[a]						16	17	18	22[a]						23	24	25					Up to 2 yrs after 1st IP dose
Hours		Relative to start of infusion														Relative to start of infusion										Relative to start of infusion									Relative to start of infusion												
	Predose	0	[redacted]	2	3	4	6	8	12	16	20	24	48	72	Predose	0	2	4	6	8	12	24	48		Predose	0	4	6	8	12	24	48		Predose	0	4	6	8	12	24	48						
INVESTIGATIONAL PRODUCT DOSING																																															
AMG 562 IV[b]		X														X										X									X												
Premedication[g]	X														X										X									X													
LABORATORY ASSESSMENTS																																															
Pregnancy test[h]	X																																													X	
Coagulation[s]	X														X										X									X											X	X	
Hem, chem[s]	X														X										X									X											X	X	
Ferritin[i]		<--- at onset of CRS, and daily until values are back to baseline/event is resolved ------------------------------>																																													
CSF analysis [o, r]		Collect if grade ≥3 neurologic event or seizure grade ≤ 2[r]																																													
Urinalysis	X														X																														X	X	
Ig: IgA, IgM, IgG	X																																												X		
Anti-AMG 562-Ab	X[j]																																													X	

Page 2 of 4

Footnotes defined on last page of this table

Table 11. Schedule of Assessments for Treatment Cycle 3 and Following to End of Study

	Treatment Period (Cycle 3 and following)																																											EoT	SFU	LTFU[c]
Cycle Day	1[b]											2	3	4	8[a]							9	10	11	15[a]						16	17	18	22[a]						23	24	25					Up to 2 yrs after 1st IP dose
Hours	Predose	Relative to start of infusion													Predose	Relative to start of infusion									Predose	Relative to start of infusion								Predose	Relative to start of infusion												
		0	[redacted]	2	3	4	6	8	12	16	20	24	48	72		0	2	4	6	8	12	24	48			0	4	6	8	12	24	48			0	4	6	8	12	24	48						
BIOMARKER ASSESSMENTS																																															
[redacted]																																															

Page 3 of 4

Footnotes defined on last page of this table

Table 11. Schedule of Assessments for Treatment Cycle 3 and Following to End of Study

	Treatment Period (Cycle 3 and following)																																												EoT	SFU	LTFU[c]
Cycle Day	1[b]											2	3	4	8[a]							9	10	11	15[a]						16	17	18	22[a]						23	24	25					Up to 2 yrs after 1st IP dose
Hours	Predose	Relative to start of infusion													Predose	Relative to start of infusion									Predose	Relative to start of infusion								Predose	Relative to start of infusion												
		0	[redacted]	2	3	4	6	8	12	16	20	24	48	72		0	2	4	6	8	12	24	48			0	4	6	8	12	24	48			0	4	6	8	12	24	48						
BIOMARKER ASSESSMENTS (Continued)																																															
[redacted]																																															
PK ASSESSMENTS																																															
AMG 562 PK[p, t]	X		X												X										X									X											X	X	
DISEASE ASSESSMENTS and RADIOGRAPHIC ASSESSMENTS																																															
PET/CT[q]																																													X		
BM aspirate/ biopsy[l]		<------------------ at EOT to confirm CR[l] ---------------->																																													

Page 4 of 4

Ab = antibody, AE = adverse event, BM = bone marrow, chem = chemistry; con meds = concomitant medications, CR = complete response, CRS = Cytokine Release Syndrome, ctDNA = circulating tumor DNA, CT = computed tomography, demo = demographics, DRE = disease-related event, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = end of treatment, Expl = exploratory, hem = hematology, Ig = immunoglobulins, LTFU = long-term follow-up, MRD = minimal residual disease, MRI = magnetic resonance imaging, neuro = neurological, NGS = next generation sequencing, ox = oximetry, PB = peripheral blood, PD = progressive disease, periph = peripheral, PK = pharmacokinetics, PR = partial response, SAE = serious adverse event, SFU = safety follow-up,

[a] The Dose Level Review Team may decide to change timing of D8/D15/D22 within a window of ± 1 day. In this case, timing of the following visits would be adjusted accordingly.

[b] In case of step-dosing, the subsequent treatments will be at weekly intervals after the target dose is administered.

[c] LTFU via on-site visit every 6 weeks until progression of disease. Afterwards, LTFU frequency will be 3 months for collecting information on survival and subsequent anti-lymphoma treatment only, without the requirement for on-site visitsThe procedures or assessments as mentioned in section 7.2.4 are applicable only if on-site visits apply.

[d] See Section 6.2.1.1 for details on hospitalization requirements.
[e] See Section 9.2.2.1 and Section 9.2.2.3 for SAE reporting requirements during LTFU.
[f] ECGs and vitals should be performed prior to any invasive procedures. ECGs are only required in treatment cycle 1 and 2. In case of intra-subject dose escalation: conduct ECGs as in cycle 1 during the first cycle after dose escalation. Starting with cycle 3, time points for vital sign measurement > 4 h after each infusions apply if the subject is still hospitalized at the time.
[g] For premedication details see Section 6.3
[h] Serum pregnancy test required at screening. For later time points, urine pregnancy test is allowed. In case of a positive result, serum pregnancy test should be repeated. Pregnancy tests will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.
[i] Ferritin assessment to be performed at onset of CRS, and daily until values are back to baseline/event is resolved.
[j] Predose anti-AMG 562 antibody sample in every 2nd cycle after cycle 1 (C1D1, C1D15 C3D1, C5D1, ..).

[redacted]

[q] PET/CT will be performed at screening, week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond. Clinical tumor assessments will be performed at screening, week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond. Every attempt should be made to complete PET and CT within 3 days of each other, particularly during treatment. If subject discontinues study treatment for any reason, including toxicity or clinical evidence of disease progression, PET/CT should be conducted 14 (+ 3) days following the last dose of AMG 562.
[r] In case of seizure of any grade perform brain MRI and cerebro spinal fluid (CSF) analysis, if there are no contraindications.
[s] As indicated in Section 7.3.10, hematology and chemistry panels include differential cell counts and comprehensive metabolic profile, as well as serum uric acid and phosphorous levels, and liver function tests. Coagulation panel includes prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen and D-dimer
[t] PK samples should be collected at the exact nominal time point specified; all times are relative to the start of infusion. The [redacted] hour sample is the same as the end of infusion and should be collected as close as possible to the end of infusion of AMG 562. If unable to collect a PK sample at the specified nominal time point, then collect the sample as close as possible and record the actual collection time. The exact date and time of IP administration and PK sample collection should be documented. Additional PK samples may be collected per the discretion of the PI as clinically indicated.

Table 12. Dosing Schedule with 48, 72, and 96 hour Step-up dosing Intervals

	Treatment Period																										
Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
No Intermediate doses	X		**T**[2]					**T**[2]							**T**[2]							**T**[2]						
	X			**T**[2]				**T**[2]							**T**[2]							**T**[2]						
One Intermediate dose	X		X[1]		**T**[2]			**T**[2]							**T**[2]							**T**[2]						
	X				X[1]				**T**[2]						**T**[2]							**T**[2]						
Two Intermediate doses	X			X[1]			X[1]			**T**[2]					**T**[2]							**T**[2]						
Three Intermediate doses	X		X[1]		X[1]		X[1]		**T**[2]						**T**[2]							**T**[2]						
	X				X[1]				X[1]				X[1]				**T**[2]					**T**[2]						

[1] Intermediate dose
[2] Target dose

7.2 General Study Procedures

A signed and dated IRB/IEC approved informed consent form (ICF) must be obtained prior to performing any study specific procedures, including discontinuing standard therapy for observing study specific washout periods.

Subjects will be seen in the clinic for study evaluations. When ECGs, vital signs, and invasive procedures like blood or BM sampling occur on the same visit, ECGs and vital signs should be collected prior to performing any invasive procedures.

Blood samples for biomarker and PK assessments should be drawn from a peripheral vein and not from a central venous catheter. The study specific lab manual will provide additional detail on lab sampling and handling requirements.

Study procedures should be performed and samples obtained at the time points stipulated in the Schedules of Assessments (Table 8 through Table 11).

Acceptable deviation windows for study procedures are listed below:

- ECGs, [redacted], safety labs, vital signs (incl. pulse oximetry):
  - ± 15 minute window if collected within the first 24 hours (excluding the 24 hour sample) after the start of an infusion
  - ± 1 hour window if collected 24 or 48 hours after the start of an infusion
- PK blood draws see Appendix I.

Starting with Day 4 post infusion, assessments should be performed on the indicated study day prior to infusion.

Acceptable deviation windows for study visits are listed below:

- Visits during treatment-free interval, if applicable: ± 1 day
- SFU: + 7 days
- LTFU: ± 7 days for on-site visits, ± 2 weeks for remote survival follow-up

Furthermore, start of a treatment can be delayed for administrative/logistical reasons for up to 7 days to allow for appropriate scheduling after discussion with and final approval by sponsor.

The DLRT may recommend a ± 1 day window for infusions following the day 1 infusion.

The DLRT may also recommend to reduce the number of infusions for a dose cohort. If no infusion was administered on Day 8, 15, and/or 22, all assessments that occur > 1 time on the respective day only have to be performed once, at any time during that day. Also, the following assessments scheduled for 24 hours, 48 hours, and 3 days post infusion would not be mandatory in that case: physical examination, vital signs,

ECG, hematology, chemistry, coagulation, urinalysis, PK and the following [redacted]

Any missed visits, tests not done, or examinations that are not conducted must be reported as such on the eCRFs. Subsequent study visits should resume on the original schedule. Missed assessments at prior visits should not be duplicated at subsequent visits. Every effort should be taken to collect all biomarker and PK samples as described in the schedule of assessments. However, if sample processing/shipment on a weekend/holiday is not logistically feasible for a site, this needs to be documented and will not be considered a deviation from the protocol.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

7.2.1 Screening

After written consent has been obtained, subjects will be screened in order to assess eligibility for study participation. All screening procedures must be performed within 21 days prior to start of investigational product administration, unless otherwise noted. The ICF may be signed earlier than 21 days prior to start of investigational product in case of washout times that have to be observed to meet eligibility criteria.

Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study. If a subject has not met all eligibility criteria at the end of the 21-day window, the subject will be registered as a screen failure. Subjects who screen fail may be eligible for re-screening at the investigator's discretion after consultation with Amgen (see also below for details on re-screening).

Laboratory assessments used to determine subject eligibility may be repeated once for confirmation during each 21-day screening period before the subject is considered a screen failure. If laboratory assessments are repeated during the screening period, the result of the last sample taken prior to start of treatment with AMG 562 will be taken into account for determination of subject eligibility.

The following procedures are to be completed during the screening period at the time points designated in the Schedules of Assessments (Table 5 through Table 8). Assessments that were performed as standard of care prior to signature of informed consent, but within 21 days prior to start of treatment with AMG 562 can be used as screening assessments and do not need to be repeated to confirm subject eligibility.

- confirmation that the ICF has been signed
- demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness

- medical history (including surgical history)
- physical examination (including neurological exam)
- ECOG performance status
- height and weight
- vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- pulse oximetry
- ECG triplicate measurement
- MRI of the brain
- Bone marrow biopsy. See Section 7.3.12.4
- Lymph node biopsy. Exceptions can be made based on site accessibility upon consultation with the Amgen Medical Monitor
- laboratory assessments: hematology, chemistry, coagulation, urinalysis, serum pregnancy test (females only and not required if surgically sterile or ≥ 2 years postmenopausal), hepatitis serology, immunoglobulins
- [redacted]
- disease assessments:
  - for all subjects: Clinical tumor and radiographic assessment (PET/CT) at screening and re[peated at week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond
- serious adverse event reporting
- documentation of concomitant medication

Re-Screening:

Subjects may be re-screened up to 2 times at the discretion of the investigator, after consultation with Amgen. The subject must be re-consented if a re-screening attempt occurs more than 30 days after the original signing of the ICF.

Re-screened subjects must be documented as screen failed in the subject's medical record and subsequently documented as re-screened. Subjects will retain the same subject identification number assigned at the time of initial screening. Once the subject is recorded as re-screened, a new 21-day screening window will begin. The following assessments do not have to be repeated during re-screening, if they were performed as standard of care or during the initial screening attempt within the time frames specified below:

- Hepatitis serology does not need to be repeated if it was performed within 6 weeks prior to start of treatment with AMG 562.
- Imaging assessments do not need to be repeated if they were performed within 4 weeks prior to start of treatment with AMG 562.

- Any other assessments do not need to be repeated if they were performed within 21 days prior to start of treatment with AMG 562.

7.2.2 Treatment

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 5 through Table 8).

Subjects will be hospitalized as outlined in Section 6.2.1.1.

Treatment begins on Day 1 when the first investigational product infusion is administered to a subject.

Prior to each start of investigational product infusion all protocol-required predose assessments including premedication have to be performed.

Results of any predose laboratory tests will not have to be available before starting the infusion with AMG 562. Laboratory assessments that were done within 24 hours prior to infusion start do not need to be repeated prior to infusion.

The following procedures will be completed during the treatment period at the times designated in the Schedules of Assessments (Table 5 through Table 8):

- hospitalization
- physical examination
- ECOG performance status
- weight
- vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- pulse oximetry
- ECG triplicate measurement
- laboratory assessments: hematology, chemistry, coagulation, urinalysis, urine/serum pregnancy test (females only and not required if surgically sterile or ≥ 2 years postmenopausal), ferritin, immunoglobulins, anti-AMG 562 antibody sample collection
- AMG 562 PK sample collection
- [redacted]
- serious adverse event reporting
- disease assessments:
  - for all subjects: Clinical tumor and radiographic assessment (PET/CT) at week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond

- adverse event reporting
- disease-related event reporting
- documentation of concomitant medication
- administration of protocol-required therapies
- For subjects to whom intra-subject dose escalation applies:
- Subjects should be hospitalized as outlined in schedule of assessment section 7.1. Hospitalization may also be required at other times (eg, intra-subject dose escalation).
- All other assessments should be performed as per the schedule of assessments applicable to the actual cycle

In case of CRS:

- Ferritin should be repeated until values are back to baseline or the event is resolved

[redacted]

7.2.3 Safety Follow-up Visit(s)/End of Study Visit

The SFU visit should occur approximately 30 (+7) days after the last dose of AMG 562. Every effort should be made to conduct this visit for all subjects enrolled into the study, including subjects who withdraw from treatment early. The following procedures will be completed during the SFU visit as designated in the Schedules of Assessments (Table 8).

- physical examination (including neurological exam)
- ECOG performance status
- weight
- vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- pulse oximetry
- ECG triplicate measurement
- laboratory assessments: hematology, chemistry, coagulation, urinalysis, urine/serum pregnancy test (females only and not required if surgically sterile or ≥ 2 years postmenopausal), anti-AMG 562-antibody sample collection
- AMG 562 PK sample collection
- disease assessments
- [redacted]
- serious adverse event reporting
- adverse event reporting

- disease-related event reporting
- documentation of concomitant medications

perform assessments driven by observation of CR/progression/relapse, or CRS as listed in Section 7.2.2.

7.2.4 Long-term Follow-up

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.

Subjects will allow Amgen continued access to medical records so that information related to subjects' health condition, including disease status and survival, may be obtained.

The following procedures will be performed during the LTFU as designated in the Schedules of Assessments (Table 8) as long as on-site visits apply.

- laboratory assessments: immunoglobulins
- disease assessments
- serious adverse event reporting (see Sections 9.2.2.2 and 9.2.2.3 for reporting requirements during the LTFU period)

perform assessments driven by observation of CR/progression/relapse, or CRS as listed in Section 7.2.2.

7.2.5 End of Study

End of study is defined as the date of the final study visit (eg, LTFU) when assessments and/or procedures are performed.

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures listed in Section 7.2.

7.3.1 Informed Consent

A signed ICF must be obtained from each subject prior to any study-mandated procedures. All subjects who are enrolled and receive investigational product treatment

should be reconsented with any updated versions of IRB/IEC approved informed consents during study participation as applicable and per institutional guidelines.

7.3.2 Demographic Data

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally, demographic data will be used to study the impact of the protocol-required therapy on biomarker variability and PK.

7.3.3 Medical History

The investigator or designee will collect a complete medical and surgical history that started 5 years prior to screening through the time of signing of informed consent. Medical history will include information on the subject's concurrent medical conditions.

Relevant medical history, including renal/urinary history (eg, subjects' reports of subjective urine output trend), antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, polyneuropathy, and infection (resolved and ongoing) will be collected. The current toxicity grade will be collected for each condition that has not resolved.

In addition to the medical history noted above, all history related to the subject's diagnosis of B-NHL (eg, date of initial diagnosis, international prognostic index and additional risk factors at diagnosis, stage at diagnosis, COO at any timepoint ifavailable [immunohistochemistry pattern, GEP/other], BCL-2 [Fluorescent in-situ.

hybridization [FISH]: translocation, immunohistochemistry expression levels], c-myc. [FISH: translocation, immunohistochemistry expression levels]) will be recorded

Lymphoma history must date back to the initial diagnosis and any response duration must be recorded.

All findings will be recorded on the medical history eCRF.

7.3.4 Prior Therapy

For prior therapies being taken for lymphoma the therapy line, name of therapeutic agent, regimen, type of therapy, start date and stop date will be collected, as well as best responses.

For radiotherapy the type of therapy, dose, site, start date and stop date will be collected.

For prior autologous HSCT, hematopoietic stem cell mobilization source, conditioning regimen, number of cells infused ($CD34^+$/kg) on day 0, date of neutrophil engraftment (first day that ANC > 0.5 x 10^9/L for 3 consecutive days), date of platelet engraftment (first day that platelets > 20 x 10^9/L), and complications need to be collected.

7.3.5 Concomitant Medication

Concomitant therapies are to be collected from informed consent until the SFU visit. After the SFU visit until EOS only anti- lymphoma therapy is to be recorded.

Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.3.6 Clinical Evaluation

7.3.6.1 Physical Examination

A complete physical examination as per standard of care will be performed by the investigator or designee at screening and at the time points specified in the Schedules of Assessments (Table 5 through Table 8). The physical examination will include general appearance, including examination of the skin, spleen, and respiratory, cardiovascular, musculoskeletal, and neurological systems. The individual performing the physical examination will characterize their findings as either normal or abnormal. Abnormal physical examination findings found during screening should be reported on the Medical History eCRF. Abnormal physical examination findings found after the subject has received investigational product will be reported on the Event eCRF.

7.3.6.2 ECOG Performance Status

The performance status will be assessed at the time points indicated in the Schedules of Assessments (Table 5 through Table 8) using the ECOG performance status scale (see Appendix F).

7.3.6.3 Height Measurements

Height (in centimeters) will be measured without shoes at screening.

7.3.6.4 Weight Measures

Weight (in kilogram) without shoes will be measured at screening and at Safety-Follow Up.

7.3.7 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Record all measurements on the vital signs eCRF.

Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position possible. The position selected for a subject should be the same throughout the study and documented on the vital signs eCRF.

The temperature location selected for a subject should be the same throughout the study and documented on the vital signs eCRF. If abnormalities are found and they are considered an adverse event, record on the Event eCRF.

7.3.8 Pulse Oximetry

Oxygen saturation will be measured using a standard pulse oximeter. The subject must be in a rested and calm state for at least 5 minutes before pulse oximetry assessments are completed.

7.3.9 Neurological Examination

7.3.9.1 Extended Neurological Examination

An extended neurological examination will be performed during screening, on day 1, day 8, day 15 and day 22 of the first cycle, on the first day of each cycle, and at the EOS as well as in case of grade ≥ 2 neurotoxicity event daily until resolution or grade ≤ 1. Subjects will be specifically queried for neurological symptoms observed in the interval since the last extended neurological examination. Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motor system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). Neurological examinations will include a writing test to detect cerebral signs. For the writing tests, patients will be asked to write down the current date and time as well as an arbitrary sentence (this should be the same sentence throughout the study). Additional neurological examinations can be performed at the discretion of the Investigator. Neurologic examination findings should be recorded on the appropriate eCRF.

7.3.9.2 Limited Neurological Examination

A limited neurological examination will be performed at time points indicated in the schedule of assessment when the patient is in clinic. The limited neurological examinations will assess impairment of orientation to time and place, occurrence of tremors as well as writing test in Section 7.3.9.1.

Patients should be instructed to perform writing tests daily and to bring the writing tests to the clinic during study visit days.

7.3.10 Electrocardiogram (ECG) Performed in Triplicate

The subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible.

ECGs should be performed in a standardized method, as triplicate single-reads, run consecutively (ie, approximately 30 seconds apart but not greater than 3 minutes apart.), and prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

The investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

7.3.11 Clinical Laboratory Tests

Table 13 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedules of Assessments (Table 8 through Table 11). All screening and on-study samples will be collected, processed and sent to the investigator local laboratory or central laboratory as applicable (see Table 13) to be analyzed by standard laboratory procedures.

The date and exact time of sample collection will be recorded in the source documents at the site (do not use the time that the samples were frozen or any other time point).

The test results are to be recorded on the eCRFs. Missed test(s) that are not done must be reported as such on the eCRFs.

Refer to the laboratory manual and/or Amgen-provided training materials for detailed collection, processing, and shipping instructions.

Table 13. List of Analytes

Local Laboratory						Central Laboratory
Chemistry	**Hematology**	**Coagulation**	**Urinalysis**	**Other**	**Neurological Safety**	
Sodium Potassium Chloride Bicarbonate (HCO_3) or Total CO_2 Total protein Albumin Calcium Magnesium Phosphorus Glucose BUN or Urea Creatinine Creatinine[a] clearance Uric acid Total bilirubin Direct bilirubin Alkaline phosphatase ALT (SGPT) AST (SGOT) Amylase Lipase LDH Ferritin CRP Haptoglobin	ANC Hemoglobin Hematocrit MCH MCHC MCV Platelets RBC WBC Differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	PT or INR PTT or aPTT Fibrinogen D-Dimer	Specific gravity pH Blood Protein Ketones Glucose Bilirubin Leucocytes esterase (WBC) Microscopic exam (only needed for positive dipstick and should include the following): Epithelial, Bacteria, Casts, Crystal, RBC, WBC	Serology (HBsAg, HBcAb, HCV Ab, HIV) Urine or serum pregnancy test[b] Immuno-globulins (IgA, IgM, IgG) BM biopsy	CSF albumin CSF red blood cells CSF white blood cells CSF flow cytometry CSF glucose CSF protein CSF neutrophils percentage CSF lymphocytes percentage CSF eosinophils percentage CSF basophils percentage CSF monocytes percentage Additional CSF viral studies as clinically indicated	Anti-AMG 562 -Antibodies PK sampling BM and PB flow cytometry [redacted] ctDNA [redacted] [redacted] Immune response Pharmaco-genetic analyses (optional)

ALT = alanine aminotransferase; ALP = alkaline phosphatase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BM = bone marrow; BUN = blood urea nitrogen; CRP = C-reactive protein; ctDNA = circulating tumor DNA; Ig = immunoglobulins; INR = international normalized ratio; MRD = minimal residual disease; LDH = lactase dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PB = peripheral blood; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cells; CSF = cerebral spinal fluid

[a] Creatinine clearance will be calculated using the Cockcroft-Gault equation: (140 - age [years] x weight [kg] x 0.85 if female) / (72 x creatinine mg/dL), adjusted for BSA by 1.73 m^2/BSA

[b] A pregnancy test will be performed locally at each site on all women unless they are surgically sterile or ≥ 2 years postmenopausal.

Additional procedures (eg, collection of an unscheduled blood sample to measure cytokine levels) deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the investigator's discretion.

7.3.11.1 Pregnancy Test

Pregnancy tests will be performed locally at each site on all women unless they are surgically sterile or ≥ 2 years postmenopausal. A serum pregnancy test should be performed at screening. During the course of the study a urine pregnancy test is allowed, a positive result should be confirmed by a serum pregnancy test.

Pregnancy tests must be performed prior to dosing with investigational product. If the pregnancy test is positive at either time point, the subject should not be given investigational product.

7.3.12 Response Assessments

The Lugano Classification will be used to assess treatment response as described in Appendix D.

7.3.12.1 Clinical Tumor Assessment

Clinical tumor assessments will be performed as indicated in the schedule of assessments and are based on changes in the size of previously abnormal lymph node groups or extranodal sites, or the appearance of new lesions suspected to represent lymphoma progression or relapse. Findings will be recorded on the clinical tumor assessment eCRF.

7.3.12.2 Radiographic Assessment

PET/CT scans with whole body images, from base of skull to mid-thigh, will be conducted. Examinations should be consistent across all timepoints at screening, week 5, week 15, week 25, and at end of treatment if end of treatment is at week 35 or beyond including: the amount of tracer, location of injection, arm location, and scan delay.

PET images should be converted to standardized uptake values maps to support comparison across timepoints and to standardize viewing conditions CT anatomical coverage: chest, abdomen, and pelvis **(and** neck **if not visualized with chest).**

If PET and CT are acquired on the same day, it is strongly recommended that PET is performed prior to the CT with IV contrast. CT only can be performed if PET is not feasible during dose escalation. PET and CT are mandatory during expansion.

PET/CT imaging data including documentation of target lesion size (s)will be entered in the eCRF during Part 1 (dose escalation) and Part 2 (dose expansion). During Part 2, PET/CT imaging data may also be sent to a central vendor.

7.3.12.3 Bone Marrow Biopsy for Disease Assessment

Bone marrow evaluation **(core biopsy with or without aspirate)** should be performed for all subjects at screening and optional at week 5 (C2D1).

[redacted]

7.3.13 Events

Adverse event and serious adverse event as well as disease-related event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF as specified in Section 9. The severity of all events will be graded according to CTCAE, version 4.0 (Appendix A) unless specified otherwise. Exceptions: CRS will be graded according to the adopted grading system referenced in Lee et al, 2014 and TLS according to Cairo-Bishop criteria (see Appendix K for details).

7.3.14 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If the subject is deceased, the date and reported case of death should be obtained.

7.3.15 Pharmacokinetic Blood Sampling

Blood samples will be obtained for determination of serum concentrations of AMG 562 from all subjects at the time points specified in the Schedule of Assessments (Table 5

through Table 11). Blood must not be drawn from the IV access or port catheter used for dosing AMG 562.

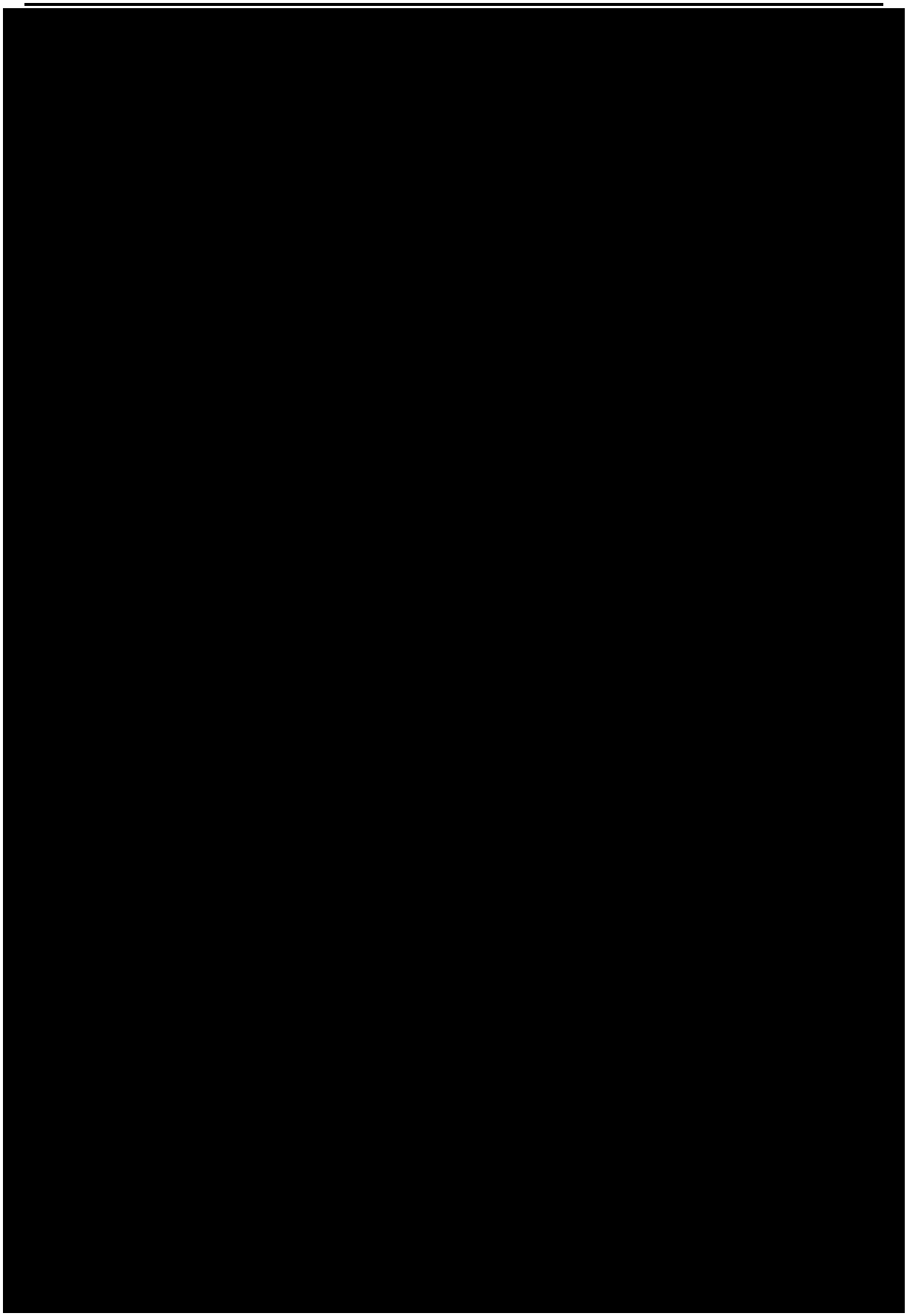
Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

7.4 Antibody Testing Procedures

Blood samples will be collected as outlined in the Schedule of Assessments (Table 5 through Table 11). Bioanalytical testing for anti-AMG 562 antibodies will be conducted on these samples only if there are unexpected PK findings or safety related concerns in the study population that warrant further investigation by characterizing drug immunogenicity. Samples testing positive may be further characterized. Additional blood samples may be obtained to rule out anti-drug antibodies during the study. Subjects who test positive for binding antibodies at the final scheduled study visit and have clinical sequelae that are considered potentially related to an anti-AMG 562 antibody response may be asked to return for additional follow-up testing.

Please see the laboratory manual for detailed sample collection and handling instructions.

[redacted]



7.7 Sample Storage and Destruction

Any blood or bone marrow sample collected according to the Schedule of Assessments (Table 8 through Table 11) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the disease, the dose response, and/or prediction of response to AMG 562 or other protocol-specified therapy, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be

made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

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

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

See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 8 through Table 11) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed

from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

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

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

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- adverse event
- death
- lost to follow-up
- decision by Sponsor
- non-compliance
- requirement for alternative therapy
- disease progression
- pregnancy

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Disease-Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease, as summarized in Table 14 below.

Table 14. Disease-related Events by System Organ Class

System Organ Class	Term(s)
Blood and lymphatic system disorders	Lymphadenopathy
General disorders and administration site conditions	Disease progression, Fatigue
Investigations	Weight decreased
Skin and subcutaneous tissue disorders	Night sweats

Disease-Related Events that do not qualify as Adverse Events or Serious Adverse Events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be recorded as a Disease-Related Event.
- Death due to the disease under study is to be recorded on the Event eCRF.

Disease-Related Events that would qualify as an Adverse Event or Serious Adverse Event:

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition, or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be recorded and reported as per section 9.1.3 as an Adverse Event or Serious Adverse Event.
- All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.

9.1.2 Adverse Events

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

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

Every increase in severity of an adverse event needs to be recorded. Record a single event for each increased level of severity on the Event eCRF. Decrease in severity only has to be recorded for DLTs and adverse events that lead to interruption of treatment/delay of a subsequent infusion.

For situations when an adverse event or serious adverse event is due to lymphoma, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer).

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

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

9.1.3 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a Disease-Related Event as defined in Section 9.1.1):

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

A Disease-Related event is to be reported as a serious adverse event if

- the subject's pre-existing condition becomes worse than what the Investigator would consider typical for a patient with the same underlying condition, or
- if the Investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-related Events

The Investigator is responsible for ensuring that all Disease-Related Events observed by the Investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/study treatment/protocol-required therapies through the Safety Follow-Up visit (ie, 30 [+7] days after the last dose of study treatment[s]) are recorded on the Event eCRF as a Disease-Related Event.

All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available

Disease-Related Events assessed by the Investigator to be more severe than expected and/or related to AMG 562/study treatment/protocol-required therapies, and determined to be serious, must be recorded on the Event eCRF as Serious Adverse Events.

Additionally, the Investigator is required to report a fatal Disease-Related Event on the Event eCRF as a Disease-Related Event.

9.2.2 Adverse Events

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

The Investigator is responsible for ensuring that all adverse events observed by the Investigator or reported by the subject that occur after first dose of investigational product(s) through the Safety Follow-Up visit (ie, 30 [+7] days after the last dose of study treatment[s]) are reported using the Event eCRF.

The Investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Toxicity grade
- Assessment of relatedness to investigational product(s) and
- Action taken.

The adverse event grading scale used will be the CTCAE Version 4.0. The grading scale used in this study is described in Appendix A. The Investigator must assess whether the adverse event is possibly related to the investigational product(s). This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)?

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

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory

findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The Investigator is expected to follow reported adverse events until stabilization or resolution.

9.2.2.2 Reporting Procedures for Serious Adverse Events

The Investigator is responsible for ensuring that all serious adverse events observed by the Investigator or reported by the subject that occur after signing of the informed consent through the Safety Follow-Up visit (ie, 30 [+7] days after the cessation of all study treatement) are recorded in the subject's medical record and are submitted to Amgen.

All serious adverse events must be submitted to Amgen within 24 hours following the Investigator's knowledge of the event via the Event eCRF.

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

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

The Investigator is expected to follow reported serious adverse events until stabilization or resolution.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically

requested, the Investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

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

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

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

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

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

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

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, Investigators should report pregnancies that occur through 110 days after the last dose of AMG 562 or in a male subject's female partner through 110 days after the last dose of AMG 562.

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

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

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

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

In addition to reporting a lactation case during the study, Investigators should report lactation cases that occur through 120 days after the last dose of protocol-required therapies.

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

- Safety: 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 Endpoints:

- 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 ($t_{1/2}$)

- Efficacy parameters:
  - ORR according to Lugano classification
  - Best overall response by category (response terminology reflects the response criteria used. 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.)
  - Duration of response (DOR)
  - Progression free survival (PFS)
  - Overall survival (OS)

Exploratory Endpoints:

[redacted]

- Incidence of anti-AMG 562 antibody formation

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 562.

The analysis of DLT will be conducted on the DLT Analysis Set defined as all subjects who are DLT-evaluable (see Section 6.2.1.3). DLT-evaluable subjects are those who 1) experienced DLTs or 2) completed DLT observational period and did not experience DLTs

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.

10.1.3 Covariates and Subgroups

The following subgroups will be used summarized safety data in part 2 of dose expansion:

- Age
  - age group: <65, ≥65; and <75, ≥75
- Sex: Male, Female
- Race
  - American Indian or Alaska Native
  - Asian
  - Black (or African American)
  - Native Hawaiian or Other Pacific Islander
  - White
  - Other
- Geographic region
  - US/Canada
  - Europe
  - Rest of the world
  - Disease state:
    - Transformed disease
    - Primary refractory disease
    - Refractory to last treatment
    - GCB versus non-GCB (Hans algorithm)
    - Double or Triple hit, vs non-double or triple hit, by FISH
  - Prior treatments
    - Autologous HSCT
    - CD19-targeted treatment

10.1.4 Handling of Missing and Incomplete Data

For efficacy data of overall response, subjects without tumor response assessments will be considered as nonresponders. Otherwise, only nonmissing data will be analyzed.

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

10.2 Sample Size Considerations

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, a subject number of 55 will provide a 43% probability of observing at least one adverse event with 1% incidence rate and 94% probability of observing at least one adverse event with 5% incidence rate. An exact 90% binomial confidence interval (CI) will be provided for overall response rate. With the 55 subjects and 40% overall response rate, the expected two-sided 90% CI would be 29% to 52%.

10.3 Adaptive Design

Details of the adaptive BLRM design are described in Appendix J.

10.4 Planned Analyses

10.4.1 Interim Analyses

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 15. The operating characteristics in Table 16 provide the probability of stopping the trial early for given hypothetical true ORR rates whereas the stopping criteria in Table 15 are based on situations where the empirical evidence would result in a posterior probability of ≥85% that the true ORR rate is ≤ 40%.

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 five weeks of treatment (with recruitment ongoing).

Table 15. 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 16. Operating Characteristics for futility 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 17. The operating characteristics in Table 18 provide the probability of stopping the trial early for given hypothetical true DLT rates whereas the stopping criteria in Table 17 are based on situations where the empirical evidence would result in a posterior probability of ≥ 90% that the true DLT rate is ≥ 33%. The evaluations could occur more frequently if necessary to address emerging safety concerns.

Table 17. 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 18. Operating Characteristics for stopping early 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**

10.4.2 Dose Level Review Team (DLRT)

Dose Level Review Meetings (DLRMs) will be held to review data, monitor safety, and make recommendations on dose escalation or / changes. The DLRT will be composed of the investigators or designees, and the following Amgen representatives: Medical Monitor/early development leader or designee, global safety officer or designee, clinical study manager, biostatistician and clinical pharmacologist. Additional members may be added as needed. The following members are responsible for DLRT recommendations: treating investigators, Amgen Medical Monitor, and global safety officer or designee before rendering final decision by Amgen.

A quorum as defined below must be in attendance for the DLRM. The quorum is defined as > 50% of the participating investigators or their qualified designee (ie, sub-investigator or research nurse or study coordinator possessing written documentation [eg e-mail] of the investigator's vote), as well as > 50% of Amgen representatives listed above. The

early development leader/medical monitor must attend for the quorum to be reached. The DLRM will be rescheduled if a quorum is not reached.

All available study data, including data collected after the initial DLT window, and including demographics, IP administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory data, efficacy and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria will be reviewed and may be considered in DLRT recommendations.

All DLRM requirements are outlined in the protocol. A DLRM Charter will not be used.

10.4.3 Primary Analysis

The primary analysis for the dose exploration part will occur when targeted enrollment is complete and each subject either completes 3 months on study or withdraws from the study. The primary analysis for the dose expansion part will occur when targeted enrollment is complete and each subject had the opportunity to receive at least 3 months of treatment.

10.4.4 Final Analysis

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

10.5 Planned Methods of Analysis

10.5.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

10.5.2 Primary Endpoint(s)

Safety Endpoints:

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the safety analysis set, which includes subjects that are enrolled and received at least 1 dose of AMG 562.

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 level. Adverse Events

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

reporting TEAEs will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

Tables of TEAEs serious TEAEs, TEAEs leading to withdrawal from investigational product or other protocol-required therapies, TEAEs that happen to ≥ 10% subjects, treatment related adverse events and fatal adverse events will also be provided.

Disease-related Events

Subject incidence of all treatment emergent disease-related events and fatal disease-related events will be provided.

Clinical Laboratory Tests

Clinical chemistry, hematology, coagulation and urinalysis data will be reviewed for each subject. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

Vital Signs

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

Physical Measurement

Physical measurement data will be listed and reviewed for each subject. Depending on the size and scope of changes, summaries of changes from baseline over time may be provided. Unscheduled assessments will be included in this summary.

Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in [QTcF, QTcB] will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage of subjects in each group will be summarized. All on-study electrocardiogram (ECG) data will be listed [and select parameters of interest plotted].

10.5.3 Secondary Endpoints

10.5.3.1 Pharmacokinetics Data Analysis

For AMG 562, PK parameters including including C_{max}, T_{max}, and AUC will be determined from the time-concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval. Based on the review of the data, analyses to describe the relationship between AMG 562 exposure and either pharmacodynamic effects and/or clinical outcome may also be performed.

10.5.3.2 Efficacy Endpoint Analyses

The following analyses will be done for all subjects in the dose exploration cohorts and the dose expansion groups. The proportion of subjects by overall response and overall response category and corresponding exact 90% CI will be calculated and tabulated for subjects treated at the MTD. 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. Overall response includes CMR and PMR.

Other efficacy endpoints includes duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

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.

PFS: PFS is calculated as the time from the date of first dose of AMG562 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.

OS: OS is calculated as the time from the first dose of AMG562 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.

Kaplan Meier curve will be presented for DOR, PFS, and OS with estimates for rates and 90% CI at selected weeks.

10.5.4 Exploratory Endpoints

[redacted]

The incidence and percentage of subjects who develop anti-AMG 562 antibodies (binding and/or neutralizing) at any time will be tabulated.

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the Investigator. The written informed consent form is to be prepared in the language(s) of the potential subject population.

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

The Investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the Investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the Investigator will be acting in that capacity, the Investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject. Non-decisional Subjects Who Require Consenting via Legally Authorized Representative Will Not be Allowed to Enroll in This Study.

11.2 Institutional Review Board/Independent Ethics Committee

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

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The Investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine

whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

12.4 Investigator Responsibilities for Data Collection

The Investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 8 through Table 11), the Investigator can search publically available records [where permitted]) to ascertain survival status. This ensures

that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

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

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

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The CTCAE version 4.0 is available at the following link:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation according to the criteria specified in Section 6.4 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4.1 and Section 6.4.2 or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

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

  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - CPK, haptoglobin, LDH, and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Sample Serious Adverse Event Form or eSerious Event Contingency Form

AMGEN Study # 20170533 AMG 562	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day_____ Month_____ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? AMG562 No/Yes; <IP/device> No/Yes; <IP/device> No/Yes; <IP/device> No/Yes	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
AMG 562	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20170533 AMG 562	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20170533 AMG 562	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20170533

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20170533

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix D. Response Assessment per the Lugano Classification

5- point scale (Deauville)

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

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

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

Appendix E. Medications That May Cause QTc Prolongation

A list of medications known to cause QTc interval prolongation is available at the following link: https://crediblemeds.org/index.php/login/dlcheck

If a participant in this study does not have access to the internet, they can contact the institution investigational pharmacy or contact their study physician to obtain a list.

Table 19 presents a list of drugs that may prolong QTc. This is not an inclusive list of drugs and is provided for guidance only. The participant is encouraged to follow the list in this link above for the most up-to-date information. Use of these drugs should be discussed with the Amgen Medical Monitor. Washout period is based on roughly 5 half-lives and rounded to a convenient interval. This list includes (but is not limited to) the following:

Table 19. Medications That May Cause QTc Prolongation

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Alfuzosin	~10 hours		7
Amantadine	17 ± 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hours (26-64)		10
Chloral hydrate	Readily converted to trichloroethanol (active metabolite $T_{½}$ = 7-10 hours)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 ± 7 hours		
Clarithromycin	Non-linear PK 3-4 hr (250 mg Q12) 5-7 hr (500 mg Q12)	36	
Chloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hours	48	
Dolasetron	8.1 hours		
Domperidone	7-8 hours	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	*Each salt form has different Half-Life*		

Page 1 of 3

Footnotes defined on last page of this table

Table 19. Medications That May Cause QTc Prolongation

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

Page 2 of 3

Footnotes defined on last page of this table

Table 19. Medications That May Cause QTc Prolongation

Compounds	Compound Half-Life	Possible Washout Period – Hours	Possible Washout Period - Days
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) $T_{½}$ = 21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only 1 datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hours	24	
Thioridazine	20-40 hours (phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenafil	4 to 5 hours		
Venlafaxine	5 ± 2 hours for parent comp. 11 ± 2 hours for OVD (active metabolite)	60	
Voriconazole	6 hours; dose dependent		
Ziprasidone	7 hours	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

Page 3 of 3

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

Sources: Drug Facts and Comparison 2006, 2005; Physician's Desk Reference, 2002; and Goodman & Gilman's the Pharmacological Basis of Therapeutics, 1996.

Appendix F. Performance Status According to Eastern Cooperative Oncology Group (ECOG) Scale

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

Source: Oken et al, 1982

Appendix G. Examples of CYP450 Substrates With Narrow Therapeutic Range

Alfentanil

Astemizole*

Cisapride*

Cyclosporine

Diergotamine

Ergotamine

Fentanyl

Pimozide

Quinidine

Sirolimus

Tacrolimus

Terfenadine*

*Not available in the US

Appendix H. Extended Neurological Examination

Abnormalities of the following should be recorded: level of consciousness, orientation, vision, cranial nerves and brain stem functions, pyramidal and extra pyramidal motory system, reflexes, muscle tone and trophic findings, coordination, sensory system, neuropsychological findings (eg, speech, cognition and emotion). Neurological examiniations will include a wrting test to detect cerebral signs. For the writing tests, patients will be asked to write down the current date and time as well as an arbitrary sentence (this should be the same sentence throughout the study).

Appendix I. Protocol Sampling Scheme (Nominal Times)

Study Day	Infusion Length (hr)	PK Draw Timepoint since Start of Infusion	Suggested PK Draw Windows
1	[redacted]	Pre-Dose	± 15 mins
		[redacted] (EOI)	
		6 hours	
		12 hours	
2		24 hours	± 1 hour
3		48 hours	
4		72 hours	
8		Pre-Dose	± 15 mins
		[redacted] (EOI)	
15		Pre-Dose	± 15 mins
		[redacted] (EOI)	
22		Pre-Dose	± 15 mins
		[redacted] (EOI)	
		6 hour	
		12 hour	
23		24 hours	± 1 hour
24		48 hours	
25		72 hours	

Appendix J. Two-parameter BLRM 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 0.90 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). Subsequent model runs may adjust the reference dose level lower or higher depending on the true DLT dose levels.

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.

Operating characteristics are described below.

Operating characteristics

The 6 planned dose levels (unit: µg) for the multiple subject cohorts were considered: [redacted] in these simulations. This assumes that the single subject cohorts execute without any safety issue.

The design was evaluated for 3 possible dose-response scenarios: "Low", "Mid", and "High" MTD. Table 20 shows the dose level and true probability of DLT for each scenario used in the simulated studies estimating the MTD. Table 21 reports the operating characteristics from 10,000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33]. Table 22 reports the operating characteristics from 10,000 simulated studies estimating the MTD when using a 3+3 design.

Table 20. True Probability of DLT by Scenario for Simulated Studies Estimating MTD

Dose Level (µg)	[redacted]					
MTD Scenario						
High	0.02	0.08	0.12	0.15	0.18	0.33
Mid	0.04	0.12	0.18	0.3	0.4	0.5
Low	0.06	0.18	0.3	0.45	0.5	0.6

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

Table 21. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD When the Target TPI is (0.20, 0.33)

MTD Scenario	High		Mid		Low	
	4 subjects per cohort	3 subjects per cohort	4 subjects per cohort	3 subjects per cohort	4 subjects per cohort	3 subjects per cohort
Number of Subjects	24	18	24	18	20	15
Median (IQR)	(20 to 28)	(1 to 3)	(20 to 24)	(15 to 18)	(16 to 24)	(12 to 18)
Number of DLTs	3	2	4	3	5	3
Median (IQR)	(2 to 4)	(1 to 3)	(3 to 5)	(2 to 4)	(4 to 6)	(3 to 4)
Proportion of DLT (%)	13	10	20	20	25	25
Median (IQR)	(10 to 17)	(6 to 14)	(15 to 23)	(14 to 22)	(20 to 29)	(20 to 28)
Percentage of studies recommending dose with DLT probability of:						
≤ 10%	2.2	2.3	2.0	2.0	6.0	7.9
> 10% and ≤ 20%	83.2	87.9	37.7	35.0	25.7	20.8
> 20% and ≤ 33%	14.6	9.5	49.9	50.7	49.1	44.7
> 33%	0	0	10.4	12.3	22.2	26.6
Probability of identifying MTD with DLT probability of >15% and ≤ 33%	54.6	53.2	81.8	77.8	74.8	65.5

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose; TPI = toxicity probability interval.

Table 22. Operating Characteristics by Scenario for Simulated Studies Estimating the MTD Using a 3+3 Design

MTD Scenario	High	Mid	Low
Number of Subjects	21	18	15
Median (IQR)	(18 to 24)	(15 to 21)	(12 to 18)
Number of DLTs	3	3	3
Median (IQR)	(2 to 3)	(2 to 4)	(2 to 4)
Proportion of DLT (%)	14	19	22
Median (IQR)	(10 to 17)	(17 to 22)	(17 to 25)
Percentage of studies recommending dose with DLT probability of:			
≤ 10%	19.4	16.0	30.4
> 10% and ≤ 20%	57.7	55.8	38.7
> 20% and ≤ 33%	0	20.53	24.5
> 33%	22.53	7.4	6.1
Probability of identifying MTD with DLT probability of >15% and ≤ 33%	25.0	54.8	63.2

DLT = dose-limiting toxicity; IQR = interquartile range; MTD = maximum tolerated dose

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

CTCAE version 4.0 classifies TLS in grade 3 (present), grade 4 (life threatening consequences; urgent intervention indicated) and grade 5 (death). Presence of TLS is not clearly defined by CTCAE version 4.0. Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). For this trial the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS (see Table 23) and clinical TLS (see Table 24) including grading as detailed below

Based on the Cairo and Bishop system, laboratory TLS is present when levels of 2 or more serum values of uric acid, potassium, phosphorus, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after initiation of treatment (Table 23).

Table 23. Cairo-bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change from Baseline
Uric acid	≥ 476 µmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mg/L	25% increase
Phosphorus	≥ 2.1 mmol/L for children or ≥ 1.45 mmol/L for adults	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Note: Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy will constitute laboratory TLS.

Clinical TLS requires the presence of laboratory TLS in addition to 1 or more of the following significant complications: renal insufficiency, cardiac arrhythmias/sudden death, and seizures (Table 24). The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 24.

Table 24. Cairo-bishop Clinical Tumor Lysis Syndrome Definition and Grading

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

Note. Laboratory TLS and at least 1 clinical complication will constitute clinical TLS.
ADL = activities of daily living, CHF = congestive heart failure, TLS = tumor lysis syndrome, ULN = upper limit of normal
[a] Not directly or probably attributable to therapeutic agent
[b] If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 µmol/L; ≥ 12 to < 16 years, both male and female, 88 µmol/L; ≥ 16 years, female 105.6 µmol/L, male 114.4 µmol/L.

Amendment 4

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

Amgen Protocol Number (AMG 562) 20170533

Amendment Date: 07 August 2019

Rationale:

This amendment contains changes to the inclusion and exclusion criteria, to the definition of a dose limited toxicity (DLT) evaluable subject, and clarifications to the Schedule of Assessments that were made based on investigator and external advisor feedback to align with clinical standards and to address the urgent treatment need of the eligible patient population. The premedication schedule was adjusted based on the dose level review meeting (DLRM) outcome of Cohort 1 review. Operational changes and changes for clarification were made.

The following updates were made to the protocol amendment 3:

- Updated language regarding dose level review meeting decisions to recommendations to align with Amgen standard processes
- Adjustment of premedication schedule based on cohort 1 DLRM recommendation and allowing oral premedication with dexamethasone to add convenience
- Adjustment of reference dose for Bayesian Model based on the observation of a DLT at an early cohort
- Restructured inclusion criteria
- Allowing prior CD19 targeting therapies except prior CD19-directed CAR-T cell therapies
- Added biopsy to SOA for subjects with prior CD19 targeting treatment
- DLT evaluable subject definition updated
- Inclusion of treatment holiday
- Revisions to Disease Related Adverse Events collection guidelines as per ASAE Adoption Committee (AAC) guidance
- Adverse event (AE) management guideline changes to improve clarity and implementation at site level
- Revisions to adverse event management section to include information on hospitalizations for AEs and restart of IP following adverse events
- PK schedule adjustments to align with ECG timepoints to fulfill QT/QTc evaluation

- Biomarker language clarification for sample collection based on disease type and study part
- Typographical and grammatical errors corrected and aligned between sections

Amendment 3

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

Amgen Protocol Number (AMG 562) 20170533

Amendment Date: 10 March 2019

Rationale:

This amendment contains changes that were requested by health authorities. In addition, it contains changes to the inclusion and exclusion criteria that were made based on investigator and external advisor feedback to align with clinical standards and to address the urgent treatment need of the eligible patient population.

The following updates were made to the protocol amendment 2:

- Language clarification:
  - Table 7. Grading and Management of Cytokine Release Syndrome.
  - Permanent discontinuation criteria for the occurrence of multiple Grade 2 or higher CRS events
  - Concomitant therapies for infection treatment
- Washout period for check-point inhibitors and monoclonal antibody-based therapy was reduced based on the aggressive disease condition. A longer washout period is not feasible as per the standard of care.
- Excluded medication for infection treatment during DLT window unless discussed with Amgen medical monitor

Amendment 2

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

Amgen Protocol Number (AMG 562) 20170533

Amendment Date: 30 November 2018

Rationale:

This amendment contains changes that were requested by health authorities and institutional review boards/ ethics committees. In addition, it contains changes to the inclusion and exclusion criteria that were made based on investigator and external advisor feedback.

The following updates were made to the protocol amendment 1:

- Typographical errors and inconsistencies between sections throughout the protocol were corrected
- Clarifications were made regarding schematics for weekly dosing to differentiate from Blincyto IP administration
- Background information was updated to reflect the recent approved therapy and benefit risk profile
- The step dosing triggers, conductance of DLRM clarified
- Premedication rules prior to IP administration updated based on HA feedback
- DLRT data review timelines for the Dose expansion clarified
- Table 8 to Table 11 (Schedule of Assessments) footnotes were updated to reflect the changes for VS and LTFU
- Several changes were made to inclusion/exclusion criteria at the request of health authorities or for streamlining purposes. The following inclusion/exclusion criteria were amended based on investigator and external advisor feedback:
  - Legally Acceptable Representatives (LAR's) removed based on EC feedback
  - Disease diagnosis clarified for DLBCL population
  - Washout period reduced for prior exposure to Rituxan based on in vitro data
- Shortening of Hospitalization requirement only after substantial amendment clarified
- Table 7. Restart guidance for Grade 3 CRS for Grading and Management of CRS events updated
- LTFU visit requirements for onsite vs. remote visits clarified
- Table 13. List of analytes updated based on lab or site performing the evaluation
- Dose Level Review Team (DLRT) language clarified

- SEC (Self Evident Corrections) removed based on recent updates within organization to remove from all protocols
- Appendix I (PK samples timepoint collection clarified based on Start of Infusion)

Amendment 1.0

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

Amgen Protocol Number (AMG 562) 20170533

Amendment Date: 20 February 2018

Rationale:

The following changes were made to the protocol dated 10 January 2018 to incorporate requested changes from FDA IND review, updates to PK, biomarker assessments and administrative clarifications:

- Updated dose regimens in the step-up dose exploration
- Modified to specify that the DLRT may prolong the dosing interval to every 2, 3 or 4 days.
- Updated to specify that enrollment in multiple subject cohorts will be staggered by 3 days.
- Updated to remove PPS and minocycline in the dose escalation portion of the protocol Section 3.1
- Revised to limit subsequent dose increases to no more than 2-fold after the occurrence of a DLT or ≥ 2 patients experiencing a Grade 2 AE.
- Revised to discontinue AMG 562 if the subject experiences Grade 3 or higher seizure on AMG 562.
- Revised to specify a Grade (eg, less than Grade 3 which resolves to Grade 2 or less) and a time to resolution for the DLT exceptions of headache and insomnia; and to include a time to resolution for the DLT exception of Grade 3 fever in Section 6.2.1.3.
- Updated to extend the DLT evaluation period to 28 days for single patient cohorts.
- Updated to remove the phrase “treatment related” from rules for transition from single subject to multiple subject cohorts.
- Updated to specify the requirement to submit a protocol amendment before administering doses > 1000 micrograms.
- Revised to clearly state that proposed changes to the DLT window will not include a shorter DLT evaluation period.
- Revise Table 7 to include the approved dose of 8 mg/kg of tocilizumab for treatment of CRS for patients.
- Revised Table 7 to state that subjects who experience Grade 3 CRS should receive steroids and tocilizumab.

- Revised to allow flexibility for use of additional medications eg, antihistamines and H2 blockers which could be administered prior to administration of AMG 562.
- Updated to remove dosing by bolus injection.
- Modified eligibility criteria to include patients with FL or MCL who have received three or more prior therapies.
- Updated Table 8 to Table 12 (Schedule of Assessments) to:
    - remove PB for MRD assessments by NGS
    - Removed some PK and biomarker assessment time points
- Updated protocol body and footnotes to reflect Table 8 to Table 12 revisions
- Corrected grammar errors throughout document.
- Updated Page numbers in Table of Contents.