Title Page

Protocol Title:		A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)
Short Protocol Title:		Open-label, Dose-escalation, and Expansion Study of AMG 340 in Subjects with Metastatic Castrate-resistant Prostate Carcinoma
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This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (International Council for Harmonisation [ICH] E6).

Confidentiality Notice

Investigator's Agreement:

I have read the attached protocol entitled A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC), dated **07 December 2022**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, 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) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 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)

_____
Title and Role of Investigator

_____
Institution Name

_____
Address and Telephone Number of Institution

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1. Protocol Summary

1.1 Synopsis

Protocol Title: A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)
Short Protocol Title: Open-label, Dose-escalation, and Expansion Study of AMG 340 in Subjects with Metastatic Castrate-resistant Prostate Carcinoma

Study Phase: 1

Indication: Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)

Study Rationale

To evaluate the safety, pharmacokinetic/pharmacodynamic (PK/PD) properties, and clinical activity of the T-cell-engaging bispecific antibodies (T-BsAb) AMG 340 in subjects with metastatic castrate-resistant prostate carcinoma (mCRPC), this study will enroll subjects with progressive mCRPC that have been exposed to 2 or more lines of therapy. In order to be eligible for this study subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel). Single-subject cohorts will initially receive AMG 340 once every 3 weeks (Q3W) beginning at a dose of [redacted] mg (based on minimum anticipated biological effect level [MABEL]); once toxicity or activity emerges, subjects will be enrolled based on Bayesian optimal interval (BOIN) design. The objective of this study is to evaluate the safety of AMG 340 as monotherapy, find the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of AMG 340, and to establish the PK and PD characteristics of AMG 340. A Q3W dosing frequency was selected for initial dosing in Part A to allow adequate time for detection of toxicity between doses, and to limit drug accumulation.

Therapeutic options for advanced mCRPC are limited. Despite the success of chemotherapy, second generation non-steroidal anti-androgens, and androgen receptor blockers, patients that progress after treatment with these therapies have few therapeutic options. Therefore, patients that have progressive mCRPC and that have been exposed to 2 or more lines of therapy are proposed as eligible subjects for this study. Subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel).

Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 340 when administered as monotherapy.	• Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs and clinical laboratory tests
• Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) for AMG 340 when administered as monotherapy.	• Dose-limiting toxicities (DLTs)

• Evaluate the pharmacokinetics (PK) of AMG 340 when administered as monotherapy.	• PK parameters of AMG 340 including, but not limited to:
	  • C_{max}
	  • Time to C_{max} (T_{max})
	  • Area under the concentration-time curve within a dosing interval (AUC_{0-t})

Secondary	
• Evaluate the clinical activity of AMG 340 when administered as monotherapy.	• Objective response (OR) per RECIST 1.1 • Overall survival (OS) • Progression-free survival (PFS) (radiographic and PSA) • 6-month landmark radiographic PFS • PSA response (30%, 50%, 70% and 90%) • Time to progression (radiographic and PSA) • Duration of response (DOR) per RECIST 1.1 • PSA DOR based on PSA50 • Time to symptomatic skeletal events (SSE)

Overall Design

This is a phase 1 open-label, dose-escalation and expansion study evaluating the safety, PK, PD, and clinical activity of AMG 340 in subjects with progressive mCRPC who have

received at least 2 or more prior lines of systemic therapy ('Line/regimen of therapy' is defined as a course of therapy [at least 1 cycle uninterrupted by progressive disease, cycle disruption due to toxicity or intolerance is acceptable]). To be eligible for enrollment in this study, subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel).

The study will consist of 2 parts: a monotherapy dose escalation (Part A; Section 4.1.1) and a monotherapy dose expansion (Part B, Sections 4.1.2).

Number of Subjects

The total number of subjects enrolled in both parts of the study is anticipated to be approximately 100 subjects (up to 60 subjects in Part A [monotherapy dose escalation] and up to 40 subjects in Part B [monotherapy dose expansion]) at sites in the US with a potential expansion to sites in Europe and the Asia-Pacific (APAC) region.

Summary of Subject Eligibility Criteria

Adult male subjects with progressive mCRPC who have received 2 or more prior lines of systemic therapy approved for the treatment of mCRPC will be enrolled. Subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel).

For a full list of eligibility criteria, please refer to Section 5.1 and Section 5.2.

Treatments

AMG 340 will initially be administered as an IV infusion Q3W, where 1 cycle of treatment will be 21 days. The starting dose of AMG 340 will be [redacted] mg administered as an IV infusion (Q3W) in Part A and escalate to a projected maximum of [redacted] mg in subsequent cohorts. In Part B, all subjects will receive AMG 340 at the MTD and/or RP2D. The dose(s) selected for evaluation in Part B may be a dose at or below the MTD defined in Part A or the RP2D. Dosing frequency for Part B will be chosen by the sponsor based on safety, tolerability, PK/PD, and clinical activity data collected from Part A, in consultation with the study investigators.

Statistical Considerations

Descriptive statistics will be provided for selected demographics, safety 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.

The proportion of subjects with an OR per RECIST 1.1 along with the corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934); similarly, the proportion of subjects, 95% CI will be tabulated for PSA response. Kaplan-Meier quartiles, rates and curves will be used to summarize OS, rPFS, 6-month landmark rPFS, PSA PFS, time to progression (radiographic and PSA), time to symptomatic skeletal events (SSE), and DOR.

Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the Safety Analysis Set, which includes subjects that are enrolled and received AMG 340. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. The statistical analysis methods for other safety endpoints are described in Sections 9.4.2.3.2 through 9.4.2.3.6.

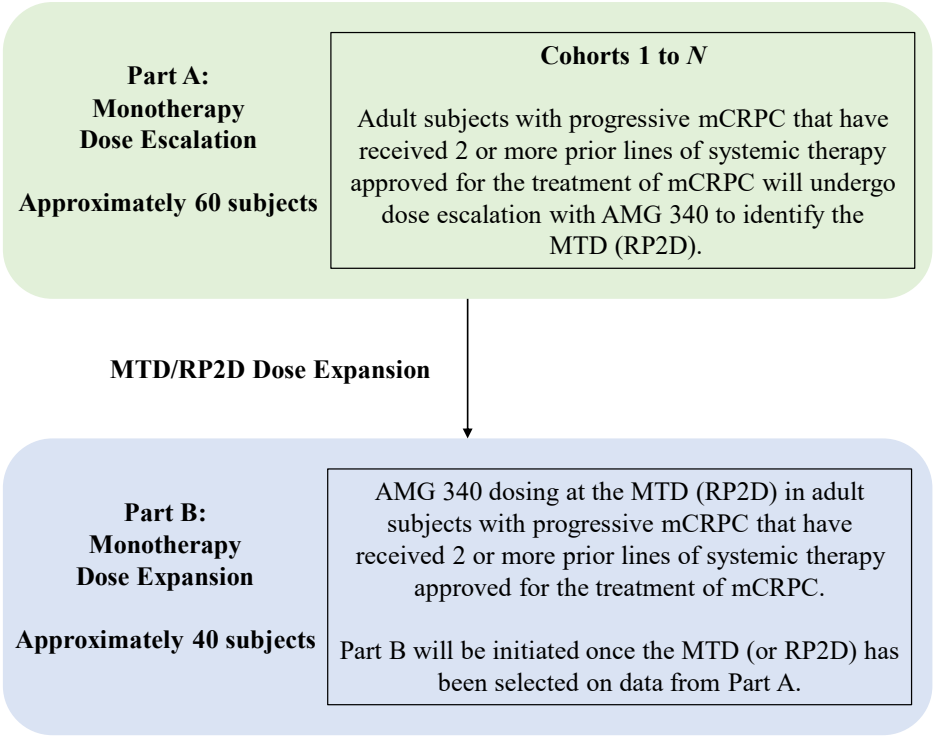
For a full description of statistical analysis methods, please refer to Section 9.

Statistical Hypotheses

In Part A, a safe and tolerable dose of AMG 340 will have evidence of anti-tumor activity in subjects with mCRPC as measured by objective response rate (ORR). In Part B, AMG 340 will improve ORR in subjects with mCRPC to 20% compared with the reference ORR of 5%.

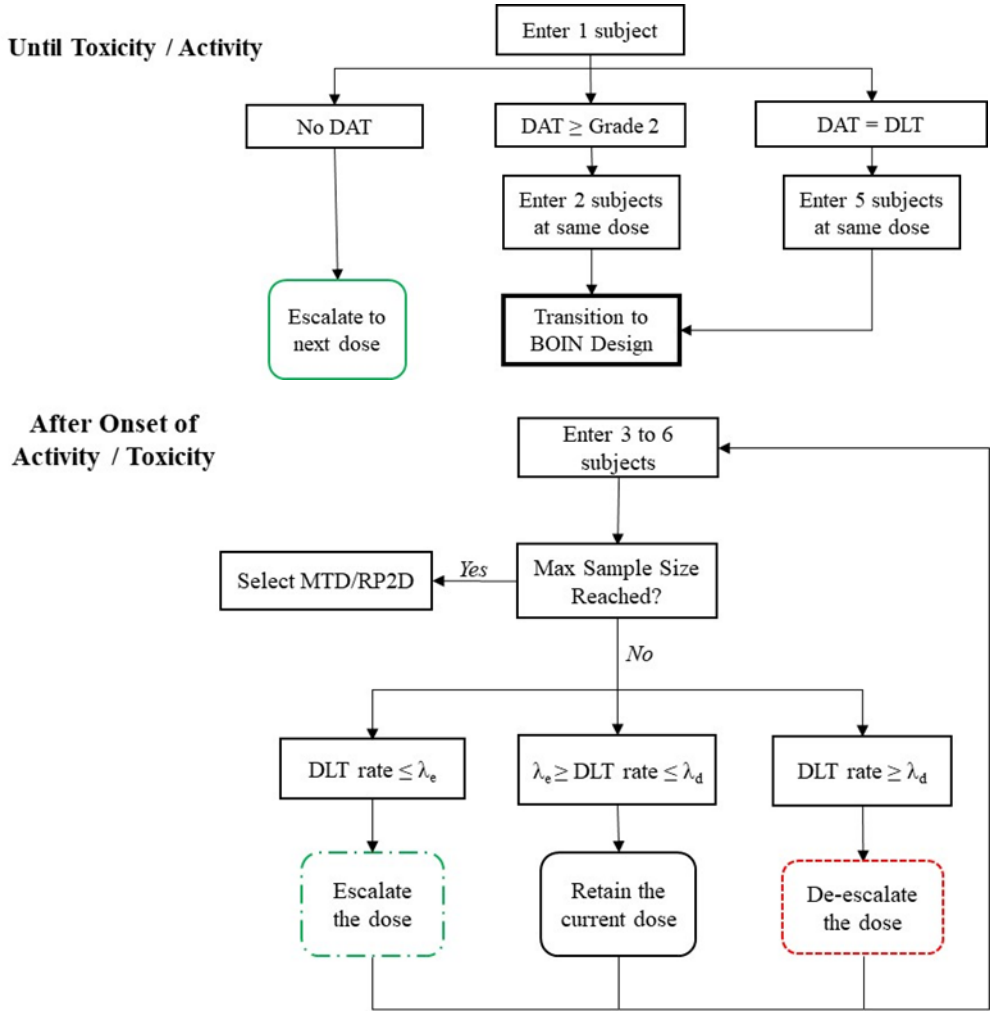
Sponsor Name: Amgen, Inc.

1.2 Studv Schema



mCRPC = metastatic castrate-resistant prostate carcinoma; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose

Figure 1-2. Part A: Monotherapy Dose Escalation



Note: The approximate number of subjects is based on lack of DATs in any cohort. The actual numbers of subjects will depend on safety and other findings.
BOIN = Bayesian Optimal Interval; DAT = drug-associated toxicity; DLT = dose limiting toxicity; MTD = maximum tolerated dose; RP2D = recommended phase 2 dose.

1.3 Schedule of Activities (SoA)

Table 1-1. Schedule of Activities

Study Activity	Screening	C1 Treatment Period DLT Window (Days 1-21)										Treatment Period (3-week cycles)										UNS Visit[a]	EOT[b]	SFU[n]	Survival FU/LTFU[o]
		W1						W2[d]			W3	C2		C3			C4 & C5	C6			C7+				
												W1	W3	W1	W2	W3	W1	W1		W3	W1		Within 30d after last dose	90d after last dose	Every 6 months
Study Day	Day -28 to Day -1	D1	D2	D3	D5	D6	D7	D8	D9	D10	D15	D1	D15	D1	D8	D15	D1	D1	D2	D15	D1				
Window			±1h	±1h	±1d	±1h	±1h	±1d	±1h	±1h	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d			+7d	±7d
Informed Consent	X																								
Incl/Excl Criteria	X	X																							
Inpatient Stay[c]		X	X	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]															
Demographics, Medical & Cancer History, Height	X																								
Complete Physical Exam	X																						X	X	
Symptom-directed Physical Exam		X	X	X	X	X[i]	X[i]	X	X[k]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X			
Weight	X	X										X		X			X	X			X				
Vital Signs[d]	X	X	X	X	X	X[i]	X[i]	X	X[k]	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECHO	X																								
12-Lead ECG	X																								
ECOG Performance Status	X	X										X		X			X	X			X	X	X	X	
Clinical Chemistry and Hematology [e]	X	X	X	X	X	X[i]	X[i]	X	X[k]	X[k]	X	X		X			X	X			X	X	X	X	
Coagulation Panel[e]	X																								
Urinalysis	X																								
Viral Screen	X																								
Testosterone	X																								
AMG 340 administration[f]		X			X			X[j]				X		X			X	X			X				
[redacted]																									
Anti-AMG 340 antibody[e]	Refer to [redacted]																								
[redacted]																									

Study Activity	Screening	C1 Treatment Period DLT Window (Days 1-21)										Treatment Period (3-week cycles)										UNS Visit[a]	EOT[b]	SFU[n]	Survival FU/LTFU[o]
		C2		C3			C4 & C5	C6			C7+														
		W1						W2[d]			W3	W1	W3	W1	W2	W3	W1	W1		W3	W1				
Study Day	Day -28 to Day -1	D1	D2	D3	D5	D6	D7	D8	D9	D10	D15	D1	D15	D1	D8	D15	D1	D1	D2	D15	D1		Within 30d after last dose	90d after last dose	Every 6 months
Window			±1h	±1h	±1d	±1h	±1h	±1d	±1h	±1h	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d			+7d	±7d
Disease Assessments[e, h]		Refer to Table 1-3																							
Adverse event collection[l]	X	Recorded from the time of consent through SFU[n]																						X	
Serious adverse event collection[m]	Continuously throughout the study																								
Concomitant medications/ therapy[p]		Recorded within 2 weeks from the first dose of study drug through SFU[n]																							
Survival																									X

ADA = antidrug antibody; D = day; D/C = discharge; DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FU = follow-up; LTFU = long-term follow-up; PK = pharmacokinetic(s); SFU = safety follow-up; $T_{1/2}$ = terminal half-life; UNS = unscheduled; W = week.

Note: Every effort should be made to keep the Schedule of Events on time for each subject.

[a] An unscheduled visit may occur at any time during the study. Study activities shown will be performed at the investigator's discretion.

[b] The EOT visit should occur within 30 days after the last dose of AMG 340. If an alternate therapy will be initiated during this period, the EOT visit should be conducted prior to the first dose of alternate therapy.

[c] Subjects will be admitted for 48 hours **after the infusion on C1D1 and, if implemented, after a second priming dose on C1D5. I**f priming dose**s are implemented,** subject**s** will **also** be admitted for 48 hours on C1D8 **(note that a second priming dose may be implemented based on emerging data)**.

[d] Vital sign measurements include measurements of diastolic and systolic blood pressure, heart rate, respiratory rate, and temperature. On day 1 dosing, vital signs should be measured prior to study drug administration (up to 10 minutes before), 30 ± 10 minutes after initiation of study drug administration, at completion of study drug administration (±10 minutes), and 1 hour ± 10 minutes after completion of study drug administration; on C1D1 and on **C1D5 and** C1D8**,** if priming dose**s** ha**ve** been implemented, vital signs should also be measured 3, 6, and 9 hours ± 10 minutes after completion of study drug administration. Vital signs should be taken after 5 minutes of sitting or lying down.

[redacted]

[f] AMG 340 will be administered intravenously by continuous infusion pump over 120 minutes (± 10 minutes) unless otherwise noted in Section 6.1 of the protocol.

[g] CCI [redacted]

[h] Samples will be collected for disease response as indicated in Table 1-3. Subjects off-treatment for reasons other than disease progression or withdrawal of consent should continue with disease response assessments as described in Table 1-3, until documented disease progression, initiation of subsequent anticancer therapy, or withdrawal (see Table 1-3).

[i] **C1D6 and C1D7 assessments will only be performed if a priming dose has been implemented on C1D5.**

[j] A dose will only be administered on C1D8 if a priming dose has been implemented.

[k] C1D9 and C1D10 assessments will only be performed if a priming dose has been implemented on C1D8.

[l] **All a**dverse events **observed by the investigator or reported by the subject that occur from the time of consent** through the **safety follow-up visit 90 (+ 7)** days after the last dose of **study drug should be reported. For subjects that start a new line of therapy before the 90 (+ 7) day follow-up visit, all adverse events should be collected and reported through 30 days post last dose of** investigational product/protocol-required therapies **or until the subject begins a new line of therapy,** whichever **occurs** later (please refer to Section 8.1.3).

[m] All serious adverse events observed by the investigator or reported by the subject that occur **from the time of consent through the safety follow-up visit 90 (+ 7) days after the last dose of study drug should be reported. For subjects that start a new line of therapy before the 90 (+ 7) day follow-up visit, all serious adverse events should be collected and reported through 30 days post last dose of investigational product/protocol-required therapies or until the subject begins a new line of therapy, whichever occurs later** (please refer to Section 8.1.3). During the survival (long-term) follow-up phase, serious adverse events (regardless of causality) that the **investigator becomes aware of will** be reported to Amgen. After end of study, serious adverse events suspected to be related to investigational product should be reported to Amgen. Please refer to Section 8.4.6.1.3.

[n] The SFU visit should occur approximately 90 (+ 7) days after the end of the last dose of AMG 340. If a new line of therapy is initiated during this period, the SFU visit should be conducted through 30 days post last dose of AMG 340 or until the subjects begins a new line of therapy, whichever occurs later.

[o] Subjects will be followed for survival and/or the commencement of subsequent cancer therapy via clinic visits, telephone, or chart review call every 6◦months from the last SFU visit for up to a maximum of 3 years.

[p] Concomitant medications/therapy should be recorded within 2 weeks from the first dose of investigational product through the SFU or 30 days after last day of the dosing interval of investigational product/protocol-required therapies, whichever is later.

CCI

[redacted]

Footnotes described on last page of table

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Footnotes described on last page of table


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[redacted]

Table 1-3. Schedule of Disease Response Assessments

	SCR	Treatment Period[a,g]	EOT	SFU	Survival FU/LTFU	Notes
MRI brain	X					All subjects must have MRI of the brain performed within 28 days prior to the first dose of AMG 340. All brain scans on protocol are required to be MRI unless MRI is contraindicated, then CT with contrast is acceptable. Subsequently, MRI brain can be performed at any time if clinically indicated per standard of care.
CT/MRI[b], bone scan[c,f], and tumor burden assessment	X	Week 1-24 Day 1 of every 3rd cycle (at C3D1 then every 9 weeks after C3D1) Week 25+ Day 1 of every 4th cycle (= every 12 weeks)	X[d]	X[d]	X[e]	CR/PR require confirmation after at least 4 weeks. Bone PD requires confirmation after at least 6 weeks. For subjects who discontinue for any reason other than radiographic disease progression, follow-up scans should occur every 3 months until documentation of disease progression per PCWG3.
[redacted]						
^{18}F-FDG PET/CT[f]	X	Every 12 weeks	X[d]	X[d]		Dose-expansion phase
PSA	X	Day 1 of every cycle	X	X		Disease assessments will be performed centrally.

^{18}F-FDG = ^{18}F-fluorodeoxyglucose; [redacted] ^{99m}Tc-MDP = ^{99m}technetium methylene diphosphonate; C3D1 = cycle 3 day 1; CR = complete response; CT = computed tomography; EOT = end of treatment; FDG = fluorodeoxyglucose; FU = follow-up; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PD = progressive disease; PET = positron emission tomography; PR = partial response; PSA = Prostate Specific Antigen; PSMA = prostate specific membrane antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SCR = screening; SFU = safety follow-up

[a] ± 7 days. Timing is based on first dose of AMG 340 (cycle 1 day 1).

[b] Responses (PR and CR) require confirmation by a repeat consecutive CT/MRI assessment no sooner than 4 weeks after the first detection of radiographical response.

[c] Per PCWG3 recommendations, the first post-treatment bone scan (at C3D1) will be used as the baseline scan with which all future bone scans are compared. To confirm disease progression by bone scan, a second bone scan must be performed at least 6 weeks after the 2nd of the 2 lesions is noted ("2+2" rule set).

[d] Radiologic imaging (CT/MRI) and bone scan scintigraphy are required at the EOT or SFU visit if the subject has not had these imaging assessments performed within 6 weeks of the visit. For PET/CT imaging [redacted] and ^{18}F-FDG), every effort should be made to acquire PET/CT scans at the EOT or SFU visit, or prior to initiation of other therapy if the subject has not had PET/CT imaging performed within 8 weeks of the visit.

[e] For subjects who discontinued treatment for any reason other than radiographic disease progression, every effort should be made to perform radiographic imaging (CT/MRI/bone scan) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of radiographic disease progression per PCWG3, clinical progression, biochemical progression, start of new anticancer therapy, or up to 3 years after the first dose of study treatment.

[f] Blood samples or tumor biopsy must not be collected until at least 24 hours after a PET/CT scan, or at least 60 hours (or 2.5 days) following a bone scintigraphy scan.

[g] Subjects off-treatment for reasons other than disease progression or withdrawal of consent should continue with disease response assessments every 12 weeks (± 7 days) until documented disease progression, initiation of subsequent anticancer therapy, or withdrawal.

2. Introduction

2.1 Study Rationale

To evaluate the safety, pharmacokinetic/pharmacodynamic (PK/PD) properties, and clinical activity of the T-cell-engaging bispecific antibodies (T-BsAb) AMG 340 in subjects with metastatic castrate-resistant prostate carcinoma (mCRPC), this study will enroll subjects with progressive mCRPC that have been exposed to 2 or more lines of therapy. In order to be eligible for this study subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel). Single-subject cohorts will initially receive AMG 340 once every 3 weeks (Q3W) beginning at a dose of [redacted] mg (based on minimum anticipated biological effect level [MABEL]); once toxicity or activity emerges, subjects will be enrolled based on Bayesian optimal interval (BOIN) design. The objective of this study is to evaluate the safety of AMG 340 as monotherapy, find the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of AMG 340, and to establish the PK and PD characteristics of AMG 340. A Q3W dosing frequency was selected for initial dosing in Part A to allow adequate time for detection of toxicity between doses, and to limit drug accumulation.

Therapeutic options for advanced mCRPC are limited. Despite the success of chemotherapy, second generation non-steroidal anti-androgens, and androgen receptor blockers, patients that progress after treatment with these therapies have few therapeutic options. Therefore, patients that have progressive mCRPC and that have been exposed to 2 or more lines of therapy are proposed as eligible subjects for this study. Subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel).

2.2 Background

2.2.1 Disease

Prostate cancer (CaP) is the most common cancer and the second leading cause of cancer death in men worldwide, with 1.6 million cases and > 350 000 deaths annually (Fitzmaurice et al, 2017). In the US, an estimated 191 930 new cases and 33 330 deaths from CaP occurred in 2019 (American Cancer Society 2020). At presentation, 76% of cases are localized, 13% show spread to regional lymph nodes, and 6% are metastatic to distant sites (National Cancer Institute [NCI] Surveillance, Epidemiology and End Results [SEER] 2020). Many men with local or locoregional disease eventually progress

to metastatic disease. The initial management of CaP is dependent on the degree of spread as well as other factors such as the Gleason grade of the tumor, patient age, comorbidities, and prostate specific antigen (PSA) levels. Based on these factors men are risk-stratified using various classification systems (D'Amico et al, 1998; Cooperberg et al, 2011; Mottet et al, 2017; Sanda et al, 2018; Gnanapragasam et al, 2016; Lukka et al, 2001; Memorial Sloan Kettering Cancer Center 2020; National Comprehensive Cancer Network [NCCN] 2022). The NCCN system stratifies men with localized disease from very low risk, where active surveillance is recommended, to very high risk where radiation and/or surgery are preferred. Once CaP has spread beyond the local environs of the prostate, systemic therapy is indicated.

First line therapy in disseminated CaP is androgen deprivation therapy (ADT) with or without radiation; however, patients invariably progress to mCRPC, defined as progression while receiving ADT and with castrate levels of testosterone (< 50 ng/dL). Therapeutic options for mCRPC are limited (Fizazi et al, 2012; Ryan et al, 2015; Scher et al, 2012; Kantoff et al, 2010; De Bono et al, 2010; Berthold et al, 2008). Thus novel, paradigm-shifting therapies in mCRPC represent an urgent unmet medical need.

2.2.2 Available Therapies for Castrate-resistant Prostate Cancer

Both first- and second-line therapy in mCRPC usually add either a second-generation non-steroidal anti-androgen (eg, enzalutamide), an androgen biosynthesis inhibitor (eg, the CYP17A1 inhibitor abiraterone), or taxane chemotherapy (eg, docetaxel or cabazitaxel) to ongoing ADT (NCCN, 2022). Other employed agents include Radium-223, the dendritic cell vaccine Sipuleucel-T, mitoxantrone, the anti-PD-1 antibody pembrolizumab, and Poly ADP Ribose-Polymerase inhibitors (PARPi). The latter two agents are deployed in the setting of mismatch repair or BRCA/ATM deficiencies in a patient's tumor, respectively. After first-line therapy, overall survival benefits are typically 5 months or less for currently approved therapies.

Therapy in the third line and beyond is often experimental and undertaken in the context of a clinical trial. Tumor vaccines and various tyrosine kinase inhibitors (eg, the AKT inhibitor ipatasertib or the c-Kit inhibitor masitinib), as well as novel androgen receptor (AR) blockers and PARPis are in development for the treatment of progressive mCRPC. A very promising area of development is targeted agents, most prominently those against prostate specific membrane antigen (PSMA). PSMA-targeted agents include antibody-drug-conjugates (ADCs), T-BsAbs, chimeric antigen receptor T-cells (CAR-Ts), and radioligand therapies (RLTs). To date, ADCs, T-BsAbs, and CAR-T therapies have

been hampered by limited activity and substantial toxicity (Bendell et al, 2020). RLTs, notably the Lutetium-177-PSMA-617 conjugate that combines a small molecule that specifically binds PSMA with radioactive Lutetium, have shown promise. In March 2022, Lutetium-177-PSMA-617 was approved by US Food and Drug Administration (FDA) for the treatment of adult patients with PSMA-positive mCRPC who have been treated with AR pathway inhibition and taxane-based chemotherapy. Lu177-PSMA-617 has shown ≥ 50% PSA decrease in approximately 40% to 60% of treated patients in multiple studies (van Kalmthout et al, 2019; McBean et al, 2019; Heck et al, 2019; Emmett et al, 2019; Hofman et al, 2018). In two small studies it was also shown that re-challenge with Lu177-PSMA-617 resulted in 37.5 to 40% of subjects achieving a PSA decrease of ≥ 50% (Yordanova et al, 2019; Gafita et al, 2019). While these results validate PSMA as an excellent target in mCRPC, repeated use of RLTs is inherently limited by maximal total radiation burden.

2.2.3 Scientific Rationale/Role of PSMA in the Disease

PSMA is an 84 kD class II membrane glycoprotein encoded by the folate hydrolase (FOLH1) gene. It is a zinc metalloenzyme that catalyzes the hydrolysis of N-acetylaspartylglutamate to glutamate and N-acetylaspartate (O'Keefe et al, 1998; Barinka et al, 2004; Rojas et al, 2002; Mesters et al, 2006), and is predominantly expressed on prostatic epithelium. Marked overexpression is observed in prostatic adenocarcinoma (CaP) and expression increases together with grade and stage (Silver et al, 1997; Olafsen et al, 2007; FDA, 2012). Overexpression also correlates with more rapid progression and risk of relapse (Perner et al, 2007; Ross et al, 2003). The high expression of PSMA in CaP coupled with largely prostate-restricted expression in normal tissue makes this antigen ideally suited to targeted CaP therapy.

Nevertheless, very weak and predominantly cytoplasmic expression of PSMA has also been described in epithelial cells of the breast, small intestine, parotid salivary gland (which also shows luminal/apical PSMA expression), and fallopian tube (Trover et al, 1995, Wright et al, 1995; Silver et al, 1997; Kawakami and Nakayama, 1997; Cunha et al, 2006; Kinoshita et al, 2006; Mhawech Fauceglia et al, 2007). According to ICH S6(R1) and others, monoclonal antibody binding to membranes is considered significant, however cytoplasmic sites are generally considered of little to no toxicologic significance (Hall et al, 2010; Leach et al, 2010). This conclusion is consistent with the toxicity profiles of existing PSMA-targeted therapeutics. The small molecule RLT Lu177-PSMA-617 has been shown to induce grade 1–2 xerostomia (dry mouth) in up to

87% of subjects (Hofman et al, 2018), but other on-target, off-tumor toxicities have not been observed. Large molecule therapies, such as those incorporating antibodies, do not show xerostomia (Tagawa et al, 2019), presumably because they are too big to cross into the luminal space where membranous parotid glandular epithelium PSMA is localized. While Lu177 PSMA 617 is also associated with significant bone marrow toxicity, this is attributed to the radioactive warhead and is not considered PSMA-specific. Overall clinical studies of PSMA-targeted therapeutics confirm PSMA as a highly CaP-specific target, especially for antibody-based therapies.

2.2.4 Amgen Investigational Product Background: AMG 340

AMG 340 binds to CD3 on human T-cells and cell-surface PSMA on CaP cells. In mixtures of human T-cells and PSMA-positive tumor cells, this simultaneous binding to CD3 and PSMA resulted in T-cell activation and potent and efficient killing of tumor cells in vitro. Furthermore, AMG 340 killed PSMA-expressing tumor cells in vivo in the presence of human T-cells, as evidenced by dose dependent tumor eradication in mouse xenograft models. T-cell activation by AMG 340 is likely to result in markedly attenuated cytokine production compared to PSMA-targeted bispecific anti-CD3 antibodies currently in clinical development. This suggests that AMG 340 may show reduced immune-mediated toxicity (such as cytokine release syndrome [CRS] and/or neurotoxicity [NT]) in human patients as compared to other T-cell redirecting therapies, thereby addressing one of the major limitations of T-cell redirecting therapy.

Despite recent advancements, and the availability of multiple therapies for the treatment of mCRPC, relapse is inevitable. Furthermore, T-cell redirecting bispecific antibodies currently in development are hampered by safety challenges related to CRS (Bendell et al, 2020; Marshall and Antonarakis, 2020). CAR-Ts have been associated with severe CRS and have seen limited adoption because of the need to administer them at certified centers, as well as challenges related to cost and manufacturing. AMG 340, with its unique mechanism, could provide an efficacious and potentially safer approach to selectively destroy PSMA-positive mCRPC cells, and represents a novel immunotherapeutic for the treatment of mCRPC.

A detailed description of the chemistry, pharmacology, efficacy, and safety of AMG 340 is provided in the Investigator's Brochure (IB).

2.2.4.1 Nonclinical Data

AMG 340 is a fully human bispecific monoclonal IgG4 antibody being developed for the treatment of mCRPC. It consists of 2 heavy and 1 light chain(s) paired using

knob-in-hole technology. Heavy chain 1 and the kappa light chain form the paratope that binds to human CD3. Heavy chain 2 is comprised of a single VH domain that targets PSMA. The nonclinical data supporting initiation of this FIH study of AMG 340 are summarized herein; for further details see the IB.

2.2.4.1.1 In Vitro Pharmacodynamics

AMG 340 mediated tumor killing and cytokine production by human T-cells in the presence of PSMA-positive and PSMA-negative cells was tested in vitro. T-cells were co-cultured with multiple tumor cell lines including PC3 (± PSMA), LNCaP, 22Rv1, and MDA-Pca-2B and increasing concentrations of AMG 340, positive control (PC), or negative control (NC) antibody in vitro. Tumor cell death and cytokine release (including IFNγ, IL-2, IL-6, IL-10, and TNFα) were assessed. The data demonstrated that AMG 340-mediated tumor killing and cytokine production were dose- and antigen-dependent and demonstrated that AMG 340 mediated killing of PSMA-expressing tumor cells with reduced cytokine production compared to a positive control antibody that contains a high affinity anti-CD3 domain.

The ability of AMG 340 to mediate PSMA-dependent activation of CD4 and CD8 T-cells was assessed in vitro. T-cells were co-cultured with either PSMA-expressing (LNCaP) or PSMA-negative (DU145) tumor cells and increasing concentrations of AMG 340, PC, or NC antibody. AMG 340 induced activation of both CD4 and CD8 T-cells comparable to the PC antibody, but with lower potency (higher EC_{50} value).

Activation of the Treg subset within activated CD4 and CD8 T-cell subsets was assessed. AMG 340 induced maximal activation of both CD4 and CD8 T-cells comparable to the PC. Relative to the PC antibody, however, AMG 340 induced significantly less Treg activation across 3 healthy donors. The ability of AMG 340 to induce equivalent T-cell activation compared to the PC antibody but with reduced Treg activation could bolster effector T-cell function and increase immune destruction of tumor targets.

In addition to T-cell activation, the ability of AMG 340 to mediate PSMA-dependent proliferation of CD4 and CD8 T-cells was assessed in vitro. T-cells were co-cultured with either PSMA-expressing (22Rv1) or PSMA-negative (DU145) tumor cells and increasing concentrations of AMG 340, PC, or NC antibody. AMG 340 induced dose-and PSMA-dependent CD4 and CD8 T-cell proliferation comparable to the PC antibody but with lower potency (higher EC_{50} value).

Overall, the data demonstrated that AMG 340 mediated efficient T-cell activation and proliferation in an antigen- and dose-dependent manner.

2.2.4.1.2 Ex Vivo Pharmacodynamics

The ability of AMG 340 to mediate tumor cell lysis of primary PSMA-positive tumor cells and the associated cytokine release was assessed. Dissociated tumor cells from de-identified prostate cancer patients were incubated with or without PBMC in the presence of AMG 340, PC or NC and assessed for tumor cell death. Supernatants were collected and assessed for secreted cytokines. AMG 340 mediated dose-dependent killing of PSMA-positive tumor cells in the presence or absence of externally added PBMC was comparable to the PC but with greatly reduced cytokine levels.

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2.2.4.1.4 Determination of MABEL

To determine the MABEL for AMG 340, data were compiled from multiple in vitro and in vivo studies (Table 2-1). The most relevant and sensitive measure of pharmacologic activity was IL-6 release by human T-cells in the presence of AMG 340 and the PSMA-expressing prostate tumor cell line MDA-Pca-2B. The EC_{50} for this assay was 5.6 nM (0.622 µg/mL) and this EC_{50} was therefore determined to be the MABEL for AMG 340.

Table 2-1. Summary of Lowest In Vitro EC50 Values and In Vivo Activity

	Readout	EC_{50} (nM)
In Vitro	Tumor Cell Killing	6.5
	IFNγ Release	19.6
	IL-2 Release	7.8
	IL-6 Release	5.6
	IL-10 Release	22.9
	TNFα Release	10.8
	T-Cell Proliferation	20.4
	T-Cell Activation	11.2
In Vivo	Readout	C_{trough} of MED (nM)
	Tumor Volume	32.1

EC50 = half maximal effective concentration; IL = interleukin; TNFα = tumor necrosis factor alpha; IFNγ = interferon gamma; MED = minimum efficacious dose; C_{trough} = trough concentration at steady state
The table above lists the lowest EC_{50} values from multiple in vitro studies as well as the C_{trough} (measured before the second dose) of the in vivo minimum effective dose (16.7 µg/mouse).

2.2.4.1.5 Pharmacokinetics

[redacted]

2.2.4.1.6 Toxicology

No cross-reactivity to CD3 or PSMA from rodent species or non-human primates is observed. Therefore, standard nonclinical toxicology studies to evaluate AMG 340 are not feasible. Evaluation of the nonclinical safety profile of AMG 340 to support clinical studies in humans included in vitro (T-cell cytotoxicity, T-cell proliferation/activation, and cytokine release assays) and ex-vivo assays (T-cell cytotoxicity and cytokine release) as described in Sections 2.2.4.1.1 through 2.2.4.1.3. Other nonclinical safety studies

conducted with AMG 340 in support of the IND included a single-dose non-GLP cynomolgus monkey PK and tolerability study of AMG 340 and a GLP tissue cross-reactivity study in a panel of normal human tissues.

The potential for off-target or unanticipated toxicity with AMG 340 were evaluated in a non GLP single-dose cynomolgus monkey PK and tolerability study. AMG 340 was administered as a single intravenous (IV) dose to male cynomolgus monkeys at nominal doses of 0, 0.1, 1 and 10 mg/kg. Based on the human equivalent dose, the active treatment doses were up to 151-times higher than the anticipated clinical starting dose of [redacted] mg. There were no test article-related changes noted in clinical observations (including appetite assessment), body weight, clinical pathology parameters (including IgG), immunophenotyping or cytokines. The PK results confirmed exposure to AMG 340 and are described in Section 2.2.4.1.5. In conclusion, AMG 340 showed no evidence of toxicity following a single IV bolus dose of up to 10.39 mg/kg.

The potential off-target cross-reactivity of AMG 340 was assessed using cryosections from a full panel of normal human tissues from at least 3 different donors. Specific AMG 340 staining in the human tissue panel included cytoplasmic staining of epithelial cells in several tissues: breast, small intestine, parotid salivary gland, fallopian tube, and prostate gland. Cytoplasmic binding of anti-PSMA antibodies via immunohistochemistry has previously been described in all of these tissues (Trover et al, 1995; Wright et al, 1995; Silver et al, 1997; Cunha et al, 2006; Kinoshita et al, 2006; Mhawech Fauceglia et al, 2007). Monoclonal antibody binding to cytoplasmic sites are generally considered to be of little to no toxicologic significance (ICH S6 [R1]). In conclusion, the observed binding to the cytoplasm of epithelial cells from various tissues is of little to no toxicologic significance and there was no unanticipated AMG 340 staining in human tissues.

2.2.4.2 Potential Risks/Toxicities from AMG 340

As previously described, AMG 340 does not recognize CD3 or PSMA in animal species commonly used in toxicology studies, including rodent, dog, and monkey. Because AMG 340 has no relevant animal species cross-reactivity and only binds to human targets, standard nonclinical toxicology animal studies to evaluate AMG 340 were not feasible.

The potential toxicities of AMG 340 were carefully considered and are summarized below. Results from the toxicology studies described in Section 2.2.4.1.6, as well as existing clinical and nonclinical safety profiles for similar therapies with the same targets (eg, anti-CD3 mAbs such as OKT3, and anti-CD3/PSMA bispecific antibodies), suggest

these potential toxicities will be addressed by the use of a MABEL approach to determine the first-in-human (FIH) starting dose (Saber 2017). In addition, monitoring and risk mitigation of known toxicities associated with previous bispecific CD3/PSMA therapies will be conducted.

2.2.4.2.1 Cross-linking CD3 with PSMA on Tumors and Potential T-cell Mediated Toxicities

Pasotuxizumab is a PSMA-targeting bispecific T-cell engager or BiTE therapy being developed for metastatic castrate-resistant prostate cancer (mCRPC). In a phase 1 study in patients with mCRPC refractory to standard therapy (N = 16), pasotuxizumab was reported to have an acceptable safety profile with decreased lymphocytes and infections as the most common adverse events grade ≥ 3 (Hummel 2019).

Results from a phase 1 trial of HPN424 (a tri-specific anti-PSMA T-cell activating therapeutic candidate) being developed for mCRPC, reported that in 7 patients one grade 3 CRS event was noted which resolved within 8 hours. Three patients reported grade 2 rigors or fevers that were clinically manageable (Bendell et al, 2020). Overall, HPN424 was considered well-tolerated with all 7 patients continuing on study and no dose-limiting toxicities (DLTs) observed.

To reduce the risk of central nervous system (CNS) **adverse event**s and CRS, AMG 340 is engineered to have reduced in vitro cytokine release (Section 2.2.4). Additionally, AMG 340 carries mutations in the Fc region that prevent Fc mediated effector function. Importantly, the potential for antibody dependent cellular cytotoxicity mediated killing of T-cells has been eliminated thus preserving T-cell function and reducing toxicity towards T-cells. The affinity of AMG 340 for PSMA is also at least 25-fold stronger than for CD3, based on cell surface binding. The potential risks of off-tumor T-cell-mediated CNS toxicity and CRS are anticipated to be reduced.

Additionally, the Schedule of Activities (Section 1.3) is designed to monitor and risk mitigate other known toxicities associated with previous bispecific CD3/PSMA therapies that include infections, tumor lysis syndrome, neutropenia, elevated liver enzymes, and leukoencephalopathy.

2.2.4.2.2 Targeting CD3

Muromonab (OKT3), an anti-CD3 murine IgG2a monoclonal antibody (mAb) previously approved for the prevention of acute organ transplant rejection, is known to result in CRS due to the activation of T-cells following administration. While it was marketed, OKT3 had a black box warning for CRS. Upon administration, OKT3 initially activates

T-cells but then blocks CD3/T-cell function, which within minutes results in a rapid reduction of circulating T-cells (CD2, CD3, CD4, CD8). Additional adverse effects of muromonab include neuropsychiatric events, neoplasias, infections, intravascular thrombosis, and hematopoietic changes. Toxicities related to T-cell depletion or T-cell inhibition by OKT3, are anticipated to be reduced for AMG 340 based on its mechanism of action, preferential activity towards PSMA expressing tumor cells, and lack of Fc effector activity (silenced IgG4).

2.2.4.2.3 Targeting PSMA

Investigational immunotherapy products targeting PSMA include mAbs, radiotherapies, CAR-Ts, and ADCs. For anti-PSMA-targeted radiotherapies, hematotoxicity predominantly due to the radioactive warhead is the main reported adverse event in the clinic (Rahbar 2018). Similarly, the observed adverse events in patients treated with CAR-Ts and ADCs appear to be related to the mechanism of action of the therapy and not a direct effect of targeting PSMA (eg, CRS in the case of CAR-T). Two products (described above), pasotuxizumab and HPN424, are most similar to AMG 340 and to date have shown acceptable safety profiles. The reported adverse events for these products (CRS, rigors, fevers, infections, decreased lymphocytes) will be monitored in the proposed clinical trial.

2.2.4.2.4 Unanticipated Toxicity

The potential for unanticipated toxicity (eg, off target or potential impurities or contaminants) with AMG 340 was characterized in the non-GLP single-dose IV PK/tolerability study in cynomolgus monkeys (RPT.NC.0045). AMG 340 was well-tolerated in this study and no unanticipated toxicity was observed.

In addition, the potential for off-target or on-target, off-tumor binding was addressed in the GLP tissue cross-reactivity study (RPT.NC.0047) using a broad panel of tissues from multiple human donors. Cytoplasmic binding in epithelial cells from various tissues was observed but is of little to no toxicologic significance.

2.2.4.2.5 Overall Nonclinical Safety Assessment

In summary, AMG 340 binds to CD3 and PSMA, which are targets with safety profiles that are well-characterized in the literature. In vitro pharmacology studies in human cells have well characterized AMG 340 (Section 2.2.4.1.1), and results demonstrate that AMG 340 has anti-tumor killing activity with reduced T-cell cytokine release. Therefore, although a nonclinical model for toxicity testing could not be developed, the potential clinical toxicities associated with AMG 340 cross-linking CD3 on T-cells with PSMA on

tumor cells can be reasonably predicted and mitigated in the proposed clinical trial based on the existing literature, the non-GLP PK/tolerability study in cynomolgus monkeys, the GLP tissue cross reactivity study, and the pharmacology studies in human cells that characterize the in vitro activity of AMG 340.

2.2.4.3 Clinical Data

The safety, tolerability, PK, and clinical activity of AMG 340 are currently being evaluated in this ongoing phase 1, open-label, dose-escalation and expansion study of AMG 340 in subjects with mCRPC. As of the safety data cutoff date of 08 March 2022, a total of 24 subjects were enrolled in the study; 1 subject did not receive investigational product. In cohort 5, a single grade 3 CRS event was observed that triggered the implementation of a priming dose per protocol Section 6.2.1.2.

All 23 subjects who received at least 1 dose of investigational product had a treatment emergent adverse event (defined as events that occurred or worsened on or after the first dose of AMG 340 until 90 days after discontinuation of AMG 340 or until the subject started another anticancer therapy, whichever occurred earlier). The most frequently reported adverse events (≥ 20% of subjects) were nausea (13 subjects, 56.5%), vomiting (12 subjects, 52.2%), CRS (9 subjects, 39.1%), diarrhea (8 subjects, 34.8%), hypocalcemia (8 subjects, 34.8%), hypomagnesemia (7 subjects, 30.4%), dysgeusia (6 subjects, 26.1%), and hypophosphatemia (5 subjects, 21.7%). Eight subjects (34.8%) had at least 1 grade ≥ 3 adverse events. Grade 3 adverse events include anemia (3 subjects, 13.0%), aspartate aminotransferase increased (2 subjects, 8.7%), and thrombocytopenia, alanine aminotransferase increased, neutrophil count decreased, cytokine release syndrome, brain abscess, failure to thrive, confusional state, hydronephrosis, and hypoxia (each 1 subject, 4.3%). One subject (4.3%) had a grade 4 adverse events of neutropenia and thrombocytopenia, and 1 subject (4.3%) had a fatal adverse event of hemorrhage (cerebral hemorrhage following a fall).

One subject (4.3%) had an adverse event leading to discontinuation of AMG 340 (grade 2 cerebrovascular accident). Eight subjects (34.8%) had serious adverse events, including cytokine release syndrome (2 subjects, 8.7%), aspartate aminotransferase increased (2 subjects, 8.7%), and alanine aminotransferase increased, thrombocytopenia, brain abscess, failure to thrive, cerebrovascular accident, hematuria, and hemorrhage (cerebral hemorrhage following a fall) (each 1 subject, 4.3%). One subject had DLT events of neutropenia and thrombocytopenia.

As of 15 February 2022, preliminary PK data for AMG 340 were available for 20 subjects with progressive mCRPC in Study 20210249. Briefly, within the evaluated target dose range ([redacted] to [redacted] mg Q3W), the serum AMG 340 exposures increased in an approximately dose-proportional manner with mean estimated terminal half-life ($t_{1/2,z}$) ranging from 4.16 to 8.57 days after a single dose.

Refer to the IB for additional information on AMG 340.

2.2.5 Non-Amgen Investigational Product Background: Imaging Products

In some countries/regions, [redacted] and ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) are investigational products administered as part of positron emission tomography (PET)/computed tomography (CT) imaging assessments in this study. PET/CT imaging will be performed only at a select subset of participating study centers.

^{68}Gallium and ^{18}F-FDG are used for in vitro radiolabeling of specific carrier molecules which have been specifically developed and are used for diagnostic imaging with PET. [redacted] and ^{18}F-FDG PET/CT are investigational imaging modalities used with increased frequency in several clinical indications including staging of intermediate-to-high -risk prostate cancer patients or restaging in patients with biochemical recurrence, showing superiority to choline PET/CT due to their higher accuracy (Kurash et al, 2020). A study by Fendler et al (2019) established high detection rates, positive predictive value, inter-reader reproducibility, and safety of [redacted] PET for localization of biochemically recurrent prostate cancer in a prospective multicenter trial meeting the primary endpoint: [redacted] PET demonstrated 84% to 92% positive predictive value at 75% overall detection rate.

Additional information will be included in the imaging manual.

2.3 Benefit/Risk Assessment

AMG 340 is a T-cell redirecting immunotherapy that exhibits robust preclinical efficacy in models of advanced mCRPC. The pharmacology, toxicology, and PK profiles of AMG 340 have been adequately characterized to support initiation of phase 1 FIH clinical trials in subjects with mCRPC at a starting dose of [redacted] mg Q3W. Taken together, these data and high unmet medical need in the proposed patient population reflect an acceptable rationale and risk for treating adult subjects with advanced mCRPC with AMG 340 in the context of a clinical trial. Refer to the IB for details.

As a FIH phase 1 study, Study 20210249 (formerly TNB585.001) has inherent risks. Patient monitoring, both clinical and via laboratory studies, necessitates more visits to the hospital and more blood draws compared to treatment with approved therapies. As there is limited information about the safety profile of AMG 340, unanticipated toxicities may occur. T-cell engaging therapies can cause immune mediated side effects that may require hospitalization, and rarely, fatal outcomes have been reported. In some circumstances these risks may even be amplified. Specifically, the risks associated with increased monitoring have been heightened by the COVID-19 pandemic that began in 2019.

Both the AMG 340 molecule and Study 20210249 are designed to minimize risk to subjects. Only subjects that are not candidates for treatment regimens known to provide clinical benefit in mCRPC are eligible to enroll. These subjects have exhausted all proven therapies to treat their cancer, and therefore the risk of not receiving an experimental therapy for which they are eligible is high. As described in Section 2.2.4, AMG 340 incorporates a unique anti-CD3 moiety selected for reduced cytokine secretion. The molecule is therefore expected to show reduced CRS, the main toxicity observed with T-cell activating-therapies. Without compromising the need for heightened subject monitoring in a clinical trial, the 20210249 Schedule of Activities was designed to minimize subject visits and inpatient stay.

Taken together, the preclinical data and study design reflect an acceptable rationale and favorable risk-benefit ratio for treating adult subjects with advanced mCRPC with AMG 340 within the context of a clinical trial. Refer to the IB for detailed data supporting AMG 340 development for the treatment of RR mCRPC.

The above benefit risk assessment supports the conduct of this clinical trial. Reference should be made to the IB for further data on AMG 340.

2.3.1 Key Risks

Based on the biological mechanism, non-clinical studies and clinical experience with AMG 340, CRS is designated as an adverse drug reaction (ADR). The key safety risks for AMG 340 are summarized in Table 2-2.

Table 2-2. Key Safety Risk for AMG 340

Safety Risk	Description
Identified Risk	
Cytokine release syndrome (CRS)	Signs and symptoms may include (but not limited to) the following: • constitutional – fever, rigors, fatigue, malaise • neurologic – confusion, headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure (refer to immune-effector cell associated neurologic syndrome [ICANS] guidance in Section 6.2.1.6.1.1) • respiratory – dyspnea, tachypnea, hypoxemia • cardiovascular – tachycardia, hypotension • gastrointestinal – nausea, vomiting, diarrhea • hepatic – transaminitis, hyperbilirubinemia • hematology – thrombocytopenia, bleeding, hypofibrinogenemia, elevated D-dimer • skin – rash
Potential Safety Concerns	
Tumor lysis syndrome	Signs and symptoms may include hyperkalemia, hyperphosphatemia, hyperuricemia, hyperuricosuria, and hypocalcemia, potentially causing lethal cardiac arrhythmias, seizures, and/or renal failure.
Gastrointestinal toxicities	Signs and symptoms may include nausea, vomiting, diarrhea, abdominal pain, gastrointestinal inflammation and ulceration; mostly associated with CRS.
Neurological toxicities	Signs and symptoms include confusional state, headache, dizziness, encephalopathy, tremor, aphasia, and syncope; mostly associated with CRS.

Clinical signs and symptoms of CRS will be continually monitored throughout the duration of the study and at the time points indicated in Schedule of Activities (Section 1.3). Refer to Table 6-6, and Sections 6.1.5, 6.2.1.6.1.1, and 11.10 for specific recommendations regarding the mitigation and management of the risk.

Coronavirus disease 2019 (COVID-19) infection may theoretically increase the signs and symptoms of CRS. Refer to Section 5.2 and section below for additional guidance related to COVID-19.

The key safety risks are described further in the AMG 340 IB.

COVID-19 Assessment

Amgen closely monitors the COVID-19 pandemic around the world. As part of this effort, Amgen performs a rigorous assessment, considering the study design, patient safety, public health risk, benefit-risk assessment, as well as the burden on country healthcare systems. Decisions are made on a study-by-study and country-by-country basis to minimize risk to patients and avoid undue burden on healthcare facilities.

Patients who display symptoms consistent with COVID-19 infections or who have tested positive for COVID-19 should contact the investigator to ensure appropriate care as well as documentation and management of study activities.

Amgen considers that it is important to continue the proposed development of AMG 340 in this study in order to advance potential therapy options for patients as rapidly as possible, while balancing this with appropriate measures to monitor and mitigate the potential impact of COVID-19.

Subjects enrolled in this study are permitted to receive vaccinations for COVID-19.

3. Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of AMG 340 when administered as monotherapy.	• Treatment-emergent adverse events • Treatment-related adverse events • Changes in vital signs and clinical laboratory tests
• Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) for AMG 340 when administered as monotherapy.	• Dose-limiting toxicities (DLTs)

• Evaluate the pharmacokinetics (PK) of AMG 340 when administered as monotherapy.	• PK parameters of AMG 340 including, but not limited to:
	  • C_{max}
	  • Time to C_{max} (T_{max})
	  • Area under the concentration-time curve within a dosing interval (AUC_{0-t})

Secondary	
• Evaluate the clinical activity of AMG 340 when administered as monotherapy.	• Objective response (OR) per RECIST 1.1 • Overall survival (OS) • Progression-free survival (PFS) (radiographic and PSA) • 6-month landmark radiographic PFS • PSA response (30%, 50%, 70% and 90%)

	• Time to progression (radiographic and PSA) • Duration of response (DOR) per RECIST 1.1 • PSA DOR based on PSA50 • Time to symptomatic skeletal events (SSE)

Exploratory	
[redacted]	
• Evaluate immunogenicity of AMG 340	• Incidence of anti-AMG 340 antibody formation

4. Study Design

4.1 Overall Design

This is a phase 1 open-label, dose-escalation and expansion study evaluating the safety, PK, PD, and clinical activity of AMG 340 in subjects with progressive mCRPC who have received at least 2 or more prior lines of systemic therapy ('Line/regimen of therapy' is defined as a course of therapy [at least 1 cycle uninterrupted by progressive disease, cycle disruption due to toxicity or intolerance is acceptable]). To be eligible for enrollment in this study, subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel). Approximately 100 subjects will be enrolled at sites in the US.

The study will consist of 2 Parts: a monotherapy dose escalation (Part A; Section 4.1.1) and a monotherapy dose expansion (Part B, Sections 4.1.2). The overall study design is described by a study schema in Section 1.2. The endpoints are defined in Section 3.

Participants in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 9.2.

Study visits and evaluations will be performed at screening and at day 1 of each cycle. Based on a 3-week cycle, additional study visits and evaluations will be performed on days 2, 3, 8, and 15 during cycle 1, on day 15 only in cycles 2 and 3, and on days 2 and 15 in cycle 6. If a priming dose **or multiple priming doses are** implemented, additional visits and evaluations will occur **during** cycle 1.

Evaluations will include physical examination, hematology, and chemistry tests prior to all study drug dosing, at the End of Treatment (EOT) visit (within 30 days after the last dose of study drug), and safety follow-up (SFU) visit. PSA will be assessed at screening and on day 1 of every cycle. Computed tomography (CT), bone scintigraphy, FDG-PET and PSMA-PET (in subjects that sign optional consent, in Part B) will be assessed at screening and then on day 1 of every third cycle. Once reliable PK data are available for AMG 340, and if $T_{1/2}$ exceeds 18 days, the 90-day post-last treatment visit may be performed at a time more remote from the last dose in order to capture PK data at $T \geq 5 \times T_{1/2}$. Adverse events, serious adverse events, concomitant medications, laboratory data, and vital signs will be assessed throughout the study.

Blood and tissue samples for evaluation of the PK and ADA (see Section 8.5 and Section 8.7, respectively) and PD (see Section 8.8) of AMG 340 will be collected at designated time points throughout the study.

4.1.1 Part A: Monotherapy Dose Escalation

Part A was initiated and employs a dose escalation design to evaluate the safety, tolerability, PK and PD profiles of single-agent AMG 340 administered Q3W. Up to 60 subjects with progressive mCRPC who have received at least 2 prior lines of therapy will be enrolled in Part A. Subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel). In Part A, cohorts have initially enrolled single subjects (Yuan et al, 2016). Proposed dose levels for AMG 340 are outlined in [redacted] but the number of dose levels tested will depend on safety, PK/PD, and activity data.

Upon the first occurrence of a grade ≥ 2 adverse event that is not unequivocally due to the subject’s underlying malignancy or other extraneous cause, the corresponding cohort, and all subsequent cohorts in Part A, will be enrolled according to a BOIN design

with the target toxicity rate of 30%. Cohorts will enroll a minimum of 3 subjects; up to 6 subjects may be enrolled concurrently (if transition from single subject cohorts to BOIN is triggered by a DLT, 6 subjects will be enrolled in that cohort). A maximum of 60 subjects will be enrolled in Part A. No more than 2 subjects should be dosed on the same day when enrolling new cohorts. Following the first assessment of BOIN dose escalation/de-escalation at a given dose level, additional subjects may be enrolled according to the BOIN criteria (Yuan et al, 2016).

If a response (partial response [PR] or complete response [CR]) is observed in a single subject cohort, cohorts enrolling thereafter will follow a BOIN design as above. The BOIN dose escalation and de-escalation boundaries (λ_e of 0.236 and a λ_d of 0.358) are shown in Table 4-1.

Table 4-1. Dose Escalation and De-escalation Boundaries

	Number of subjects treated at current dose cohort									
Actions	1	2	3	4	5	6	7	8	9	10
Escalate if # of DLTs ≤	0	0	0	0	1	1	1	1	2	2
De-escalate if # of DLTs ≥	1	1	2	2	2	3	3	3	4	4

DLT = dose limiting toxicity
Source: Yuan et al, 2016

Dose escalation has been started as planned with a Q3W dosing schedule, which may be altered after cumulative review of safety and PK data and a protocol amendment. Administration of the first dose of AMG 340 to the first subject in each cohort must await completion of the first cycle (3 weeks) of the prior dose level, and a review of the safety data by the Dose Level Review Team (DLRT) (formerly referred to as the Safety Monitoring Group [SMG] – see Section 11.3). Input from biostatistical, PK and other

experts will be sought as necessary. Cohorts *N*a (where N represents a Cohort number), b, c, etc, may be conducted in parallel. Not all dose level cohorts may be enrolled based on emerging safety data.

Based on the DLRT's ongoing review of emerging safety, PK/PD and clinical activity data, cohorts receiving intermediate doses between those proposed above may be implemented. Furthermore, it may become necessary to switch to an alternative dosing regimen. If the dosing schedule is switched, no dose modification should result in a predicted steady state C_{max} or AUC greater than that identified for the immediately prior lower dose level.

4.1.2 Part B: Monotherapy Dose Expansion

Part B will evaluate the MTD (or RP2D) of AMG 340 monotherapy in up to 40 subjects with biopsy-proven progressive mCRPC. To be eligible for this study, subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel). Part B will be initiated once the MTD (or RP2D) has been selected based on data from the Part A. The MTD (or RP2D) and dosing frequency for Part B will be chosen by the DLRT based on safety, tolerability, PK/PD, and clinical activity data collected during the dose escalation portion of the study.

4.2 Patient Input into the Study Design

Patient input was not obtained pertaining to study design.

4.3 Justification for Dose

4.3.1 Justification for Investigational Product Dose

4.4 End of Study

An individual subject is considered to have completed the study if they have completed the last visit shown in the Schedule of Activities (Section 1.3). The total study duration for an individual subject will vary as subjects may continue to receive AMG 340 as long as they do not meet any criteria for subject discontinuation (see Section 7.1).

The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), including any additional parts in the study (eg, long-term follow-up, antibody testing), as applicable.

5. Study Population

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).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject must be ≥ 18 years of age at the time of signing informed consent.

102 Subject has a history of pathologically confirmed prostatic adenocarcinoma.

103 Subject has history of metastatic disease.

104 Subject is chemically or surgically castrate (testosterone ≤ 0.5 ng/mL or 1.7 nmol/L). Subjects must continue on an LHRH/GnRH agonist or antagonist while on study unless they are surgically castrate.

105 Subject has received at least 2 lines of systemic therapy approved for mCRPC, with disease progression on the most recent systemic therapy as defined in PCWG3. Subjects should have previously been exposed to, intolerant of, ineligible for, or declined therapy with both a novel anti-androgen (eg, abiraterone, enzalutamide) and a taxane (eg, docetaxel).

106 Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2 (see Section 11.8).

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

108 Subject must have adequate bone marrow function, defined as: absolute neutrophil count (ANC) ≥ 1500/mm^3; platelets ≥ 100 000/mm^3 (without platelet transfusion within 7 days from screening assessment); hemoglobin ≥ 9.0 g/dL (without blood transfusion within 7 days from screening assessment).

109 Subject must have an eGFR ≥ 50 mL/min as estimated by the MDRD formula. Note: Per FDA draft guidance, 'renal impairment is not likely to alter PK enough to justify dosage adjustment' for protein therapeutics > 69 kDa, specifically including antibodies, such as AMG 340 (FDA 2020).

110 Subject must have total bilirubin ≤ 1.5 × upper limit of normal (ULN; except if the subject has a known diagnosis of Gilbert's syndrome, in which case bilirubin must be < 3 × ULN). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) must be ≤ 3 × ULN (except if the subject has a known diagnosis of Gilbert's syndrome or liver metastases, in which case AST/ALT must be < 5 × ULN).

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

201 Subject has been diagnosed with or treated for another malignancy within the past 2 years whose natural history or treatment may interfere with the safety or efficacy assessment of the investigational regimen. Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

Exception(s) to the above include:

- malignancy treated with curative intent and with no known active disease present for ≥ 2 years before enrollment and judged to be at low risk for reoccurrence by the treating physician

- adequately treated non-melanoma skin cancer or lentigo malignancy without evidence of disease
- adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

202 Pathological finding consistent with pure small cell, neuroendocrine carcinoma of the prostate or any other histology different from adenocarcinoma.

203 Subject has a history of CNS involvement by their mCRPC. Metastases stemming from bone are allowed.

204 Subject has clinically significant CNS pathology. Examples include spinal cord compression, epilepsy, stroke, severe brain injury, dementia, neurodegenerative disorder, or severe mental illness. If the subject has a history of clinically significant spinal cord/nerve compression the subject must be neurologically stable for ≥ 21 days without steroid treatment prior to dosing with AMG 340 to be eligible.

205 Currently receiving treatment in another investigational device or drug study, within 5 x $T_{1/2}$ (of that agent) or less than 28 days since ending treatment on another investigational device or drug study(ies), whichever is shorter. Other investigational products/procedures while participating in this study are not permitted.

206 Subject requires chronic immunosuppressive therapy (including steroids > 10 mg prednisone/day or equivalent). At the discretion of the Medical Monitor and the sponsor, subjects may be eligible if immunosuppressive therapy is discontinued 14 days or 5 half-lives prior to the first dose of study treatment (whichever is shorter).

207 Subject has any medical or psychiatric condition which, in the opinion of the investigator or Medical Monitor, places the subject at an unacceptably high risk for toxicities, could interfere with successful or safe delivery of therapy, or could interfere with evaluation of the investigational product or interpretation of subject safety or study results. Examples include history of significant mucosal/internal bleeding within 3 months prior to the first dose of study treatment, major psychiatric illness, drug abuse (including active alcoholism), active graft versus host disease, or known allergy or hypersensitivity to components of the study drug formulation.

208 Subject has received any therapy to treat cancer (including, chemotherapy, biologics, or cellular therapies) other than therapy to maintain chemical castration or undergone a major surgical procedure within 28 days, or within 5 half-lives of an anticancer drug, prior to the first dose of study treatment, whichever is shorter. Subject who has received radiation therapy within 4 weeks of first dose (or local or focal radiotherapy within 2 weeks of first dose with the exception of radiotherapy for palliative care, such as bone pain; this is only permitted after discussion with Amgen Medical Monitor) of study treatment (cycle 1 day 1).

209 Subject has known active infection requiring parenteral antibiotic treatment. Upon completion of parenteral antibiotics and resolution of symptoms, the subject may be considered eligible for the study from an infection standpoint.

NOTE: Simple urinary tract infections and uncomplicated bacterial pharyngitis are permitted if responding to active treatment and after consultation with

Medical Monitor. Screening for chronic infectious conditions is not required unless otherwise noted as exclusion criteria.

220 Subject with symptoms and/or clinical signs and/or radiographic signs that indicate an acute and/or uncontrolled active systemic infection within 10 days prior to the first dose of investigational product administration.

210 Major cardiac abnormalities, such as but not limited to the following: uncontrolled angina or unstable life-threatening arrhythmias, history of myocardial infarction and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of AMG 340, severe cardiac insufficiency, or QTc prolongation > 470 msec (Fridericia).

211 Subject has unresolved adverse events ≥ grade 2 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0) from prior anticancer therapy except for:

- Alopecia.
- Vitiligo.
- Subjects with irreversible toxicity not reasonably expected to be exacerbated by any of the investigational products (eg, hearing loss) may be included after consultation with the Medical Monitor.

212 Positive/non-negative test for Human Immunodeficiency Virus (HIV)

213 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: hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable hepatitis B virus DNA suggests occult hepatitis B.
- Positive Hepatitis C virus antibody (HCVAb): hepatitis C virus RNA by PCR is necessary. Detectable hepatitis C virus RNA suggests chronic hepatitis C.

215 Male subjects with a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use contraception during treatment and for an additional 6 months after the last dose of investigational product. Refer to Section 11.5 for additional contraceptive information.

216 Male subjects with a pregnant partner who are unwilling to practice abstinence or use a condom during treatment and for an additional 6 months after the last dose of investigational product.

217 Male subjects unwilling to abstain from donating sperm during treatment and for an additional 6 months after the last dose of investigational product.

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

219 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

5.3 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 11.3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

Each subject who enters into the screening period for the study (as the point when the subject signs the ICF) receives a unique subject identification number before any study-related activities/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 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.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria, and the subject receives the first dose of study drug. The investigator is to document this decision and date, in the subject's medical record and in/on the Subject Enrollment case report form (CRF).

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Refer to Section 8.1.1.

6. Study Intervention

Study intervention is defined as any investigational product(s), non-investigational product(s), placebo, combination product(s), or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

A summary of the dosing and administration of each treatment is shown in Table 6-1 below.

6.1 Study Interventions Administered

6.1.1 Investigational Products

Table 6-1. Investigational Products

	Amgen Investigational Product:[a]
Study Treatment Name	AMG 340
Dosage Formulation	The AMG 340 drug product (active) will be provided as a solution in vials, formulated at 5 mg/mL with 20 mL of extractable volume of drug product per vial.
Unit Dose Strength(s)/	5 mg/mL
Dosage Level(s)	See [redacted] for proposed doses
Route of Administration	IV QW3
Accountability	The total volume of preparation, amount of investigational product used in preparation, total volume (mL) administered, start date/time, stop date/time, and lot number are to be recorded on each subject's CRF(s).
Dosing Instructions	AMG 340 will initially be administered as an IV infusion Q3W, where 1 cycle of treatment will be 21 days. The starting dose of AMG 340 will be [redacted] mg administered as an IV infusion (Q3W) in Part A and escalate to a projected maximum of [redacted] mg in subsequent cohorts [redacted] In Part B, all subjects will receive AMG 340 at the MTD and/or RP2D. The dose(s) selected for evaluation in Part B may be a dose at or below the MTD defined in Part A or the RP2D (see Section 6.2.1.1). Dosing frequency for Part B will be chosen by the sponsor based on safety, tolerability, PK/PD, and clinical activity data collected from Part A, in consultation with the study investigators. The first AMG 340 infusion will be given over 2 hours (± 10 minutes). If no infusion reactions occur during the first dose of AMG 340, the duration of infusion for subsequent doses of AMG 340 may be shortened to 1 hour thereafter. Subjects will be admitted for 48 hours after the first infusion on **cycle 1** day 1 **and, if implemented, after a second priming dose on cycle 1 day 5**. If priming dose**s are** implemented, subjects will also be admitted for 48 hours on cycle 1 day 8 (note that a second priming dose may be implemented based on emerging data). Subjects will be closely monitored for 2 hours after each infusion in all other cycles.
Dosage Preparation	Study drug will be prepared in a single dilution step, with dose dependent volumes of AMG 340 transferred from drug product vial directly into a suitable IV bag. The diluent is saline with IVSS added prior to the addition of active AMG 340 drug product. For all cohorts, total storage time (including infusion time) of the IV bag containing the [redacted] to minimize degradation of the drug product and the risk of microbiological contamination. The storage time may be updated as additional sterility/stability data become available. The total volume administered at each dose will be 250 to 500 mL. Infusion rates will be controlled with infusion pumps and their respective DEHP-free infusion sets containing inline filters. AMG 340 drug product vials are stored at 5 ± 3ºC. The IVSS vial is stored at ambient temperature. [redacted]

BID = twice daily; CRF = case report form; DEHP = Di(2-ethylhexyl) phthalate; IM = intramuscular; IV = intravenous; IVSS = Universal IV solution Stabilizer; MTD = maximum tolerated dose; NA = nonapplicable, PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous; RP2D = recommended phase 2 dose; QD = once daily; Q3W = every 3 weeks

[a] AMG 340 will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

6.1.2 Non-Amgen Investigational Imaging Products

^{18}F-FDG (in some countries/regions when used for prostate cancer) and [redacted] (in countries where it is approved as a diagnostic agent) are non-Amgen investigational products administered as part of PET/CT imaging assessments in this study.

6.1.3 Non-investigational Products

Not applicable for this study.

6.1.4 Medical Devices

There are no investigational medical devices in this study. Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-Amgen non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.1.5 Other Protocol-required Therapies

All other protocol-required therapies including, dexamethasone, diphenhydramine, acetaminophen, ranitidine, tocilizumab (or siltuximab if tocilizumab is not available), 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.

Subjects will be premedicated twice with dexamethasone. Subjects will be premedicated with dexamethasone (10 mg PO or IV) or equivalent 12 to 16 hours prior to AMG 340 administration, and then again with dexamethasone 10 mg IV or equivalent within 1 hour or AMG 340 administration. If a subject does not experience an infusion-related reaction (IRR) or an immune-mediated toxicity (IMT; eg, CRS or NT) in a given cycle, the dexamethasone premedication dose may be reduced to 5 mg IV. If a subject does not experience an IRR or IMT in a cycle where they received 5 mg dexamethasone IV as premedication, dexamethasone may subsequently be omitted from the premedication regimen. If a subject experiences an IRR or IMT at any time, or if the subject undergoes an intra-subject dose escalation, they should be premedicated with 10 mg dexamethasone with the next dose of AMG 340 and tapered as described above.

Subjects will also routinely be premedicated with diphenhydramine (25 to 50 mg IV) or equivalent (eg, cetirizine 10 mg orally [PO] x 1), acetaminophen 650 to 1000 mg PO,

and ranitidine 150 mg PO/IV or equivalent, 15 to 60 minutes prior to AMG 340 infusion to reduce the risk and severity of hypersensitivity reactions commonly observed with mAb therapy. Subjects may also be premedicated with tocilizumab (8 mg/kg IV) at the discretion of the investigator and after approval by the Medical Monitors.

Sites are required to have tocilizumab or siltuximab (if tocilizumab is not available) on site for potential treatment of CRS. For administration of dexamethasone or tocilizumab after occurrence of CRS, follow guidance in Table 6-6. Tocilizumab should be administered according to local prescribing information. If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of cytokine release syndrome, following the criteria outlined in Table 6-6. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (Sylvant Prescribing Information), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of AMG 340. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab.

6.1.6 Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging drug containers, delivery systems, labeling, and inserts.

This includes any investigational/non-investigational product(s) or combination product(s) provisioned and/or repackaged/modified by Amgen:

- AMG 340

Any product complaint(s) associated with an investigational product(s), non-investigational products(s), or combination product(s) supplied by Amgen are to be reported.

6.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

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

- any anticancer agents other than AMG 340, such as:
  - chemotherapy, biologics, cellular, or hormonal therapies (other than therapy to maintain chemical castration)
  - anticancer medicinal/herbal remedies
  - radiation therapy (within 4 weeks of first dose, or local, or focal radiotherapy within 2 weeks of first dose with the exception of radiotherapy for palliative care, such as bone pain; this is only permitted after discussion with Amgen Medical Monitor)
  - immunosuppressive therapy (except if discontinued 14 days or 5 half-lives, whichever is shorter, prior to the first dose of study treatment at the discretion of Medical Monitor and Sponsor)
- any other investigational agent with the exception of [redacted] and ^{18}F-FDG (refer to Section 6.7.2.1 for exclusionary vaccine considerations)
- plasmapheresis should not be performed while a subject is participating in Study 20210249
- intravenous immune globulin should not be given to a subject within 48 hours (before or after) of AMG 340 administration
- live and live-attenuated vaccines **are prohibited** within 28 days prior to the first dose of **investigational product and during treatment with investigational product**
  - **live viral non-replicating vaccine (eg, Jynneos) for Monkeypox infection is allowed during the study in accordance with local standard of care and institutional guidelines**
- any major surgical procedures (upon consultation with Medical Monitor)

6.2 Dose Modification

6.2.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

6.2.1.1 Dose Escalation and Selection of the MTD/RP2D Dose

DLT criteria (see Section 6.2.1.4.1) will be used to make decisions regarding dose escalation. Dose escalation decisions will be based on clinically significant toxicity, DLT events and clinical pharmacology findings, and will be made by the DLRT. A simple majority of the DLRT is required to proceed with dose escalation; for quorum requirements, see Section 11.3.

Dose escalation will be based on the BOIN escalation/de-escalation criteria described above (and as illustrated in Yuan et al, 2016; Figure 1-2), with a target toxicity rate of 30% (λ_e of 0.236 and a λ_d of 0.358). The MTD will be identified via isotonic regression of pooled escalation cohort data (Table 4-1), according to the BOIN method (Yuan et al, 2016). An expansion dose (eg, RP2D) may be selected by the DLRT prior to the identification of the MTD based on an assessment of available safety, PK/PD, and activity data; in this case the DLRT will also decide whether dose escalation in Part A should continue in parallel. Additional priming doses and intermediate dose levels may

be investigated based on emerging safety, PK, PD, and efficacy data to identify the minimum safe and biologically effective dose (MSBED) [redacted]

When the DLRT completes their safety review of cycle 1 for a Cohort N (where N represents a Cohort number), and if that dose is deemed safe (eg, the DLRT endorses further dose escalation or the dose for Cohort N is determined to be the RP2D), any subjects that remain on study at a lower dose of AMG 340 may subsequently be treated at the dose assigned to Cohort N (eg, when the DLRT review for Cohort 5 is complete and the decision to escalate to Cohort 6 has been made, any subjects still on study from Cohorts 1 to 4 may have their dose increased to the dose corresponding to Cohort 5). Subject eligibility for such an escalation must be approved by the Medical Monitor(s) and treating investigator and will be determined on a case-by-case basis. At a minimum, to be eligible subjects must have previously received at least 2 cycles of AMG 340 at their current dose without any drug related toxicities that led to a dose reduction.

6.2.1.2 Dose Priming

Based on the nonclinical pharmacology of AMG 340, a lower rate of CRS is anticipated than with other T-cell-engaging bispecifics; however, based on the mechanism of action of AMG 340, the most likely DLT to occur is still CRS ≥ grade 3. Cytokine release syndrome will be managed per Principal Investigator discretion and institutional guidelines (a guide for management of CRS is provided in Table 6-6 if institutional guidelines have not been established). Definitions for adverse events, serious adverse events, and DLTs are provided in Section 8.4.6.1.1, 8.4.6.1.2, and 6.2.1.4.1, respectively.

If a grade ≥ 3 CRS event occurs in Cohort N (where N represents a Cohort number) during the DLT period, or at the discretion of the DLRT, a dose equal to or less than the dose for Cohort N will be designated as the 'Priming Dose' and dose administration in subsequent cohorts (Cohorts N+1 and on) may be modified as follows:

- On Cycle 1 Day 1, subjects will receive the Priming Dose.
- On Cycle 1 Day 8, subjects will receive the full dose corresponding to the cohort in which they have been enrolled.

Note: a second priming dose may be introduced based on emerging data.

If a subject experiences CRS grade ≥ 2, or any other grade ≥ 2 toxicity after receiving a priming dose that is not unequivocally due to the subject's underlying malignancy or other extraneous cause, administration of the full dose on cycle 1 day 8 must await approval by the Amgen Medical Monitor**(s)**. At a minimum, CRS must have resolved to

grade ≤ 1 before the next is administered. The dose and timing of the full dose for such a subject may be modified at the discretion of the Amgen Medical Monitor and the Investigator; if the subject has their full dose reduced in cycle 1, the subject will be considered DLT-unevaluable and should be replaced. In subsequent cycles, subjects will receive the full dose on day 1.

Following implementation of a priming dose, if administration of the full dose is delayed in cycle 1, the DLT period for that subject should be extended to the same degree (eg, if the full dose is delayed by 4 days, the DLT period will also be extended 4 days). For clarity, treatment-emergent adverse events meeting criteria for a DLT will be treated as a DLT whether they occur after administration of the priming or the full dose.

6.2.1.3 Dose Cohort Stopping Rules

6.2.1.3.1 Safety

In Part A, the occurrence of DLTs will drive identification of the MTD and/or RP2D in line with standard practices in an FIH phase 1 study, as outlined in Figure 1-2. If in aggregate > 33% of subjects in Part A experience an unacceptable toxicity, including those that occur outside the DLT window, accrual will be suspended. Enrollment may be re-initiated following a review of all available data by the DLRT and consultation with FDA.

In Part B, accrual to a part will be suspended if > 33% of subjects (ie, > 10 of the planned 40 subjects in Part B) to be enrolled in that part experience unacceptable toxicity. The final decision on suspension of enrollment will be made by the DLRT following review of all available data when the stopping rule threshold is exceeded.

6.2.1.4 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. The table of clinical toxicity grades from the NCI-CTCAE, Version 5.0 (available on CTEP home page: http://ctep.info.nih.gov) is to be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events, each of which will be followed to satisfactory clinical resolution, except for CRS and NT which will be graded according to Lee et al (2019). AMG 340 has not been tested clinically in humans, so the adverse event profile in humans is not known.

Adverse events should be classified as pre-existing or as treatment-emergent adverse events:

- A treatment-emergent adverse event is defined as an adverse event not present prior to initiation of AMG 340 treatment, or an adverse event present prior to AMG 340 initiation that worsens in intensity and/or frequency after initiation of AMG 340 treatment.
- A pre-existing adverse event is an adverse event that does not meet these criteria. Subjects with pre-existing adverse events should be assessed for any underlying illness or other causes and treated as appropriate.

Subjects with treatment-emergent adverse events should also be assessed for intercurrent illness or other causes and treated as appropriate. If a treatment-emergent adverse event is unequivocally due to a subject's underlying malignancy or other extraneous cause, dosing with AMG 340 may be modified at the discretion of the Principal Investigator, following discussion with the Medical Monitors. If a treatment-emergent adverse event is not unequivocally due to the subject's underlying malignancy or other extraneous cause, regardless of whether there is a 'reasonable possibility' that the treatment-emergent adverse event is AMG 340-related, the dose of AMG 340 should be modified as follows:

- For subjects who have completed cycle 1 and have at least clinically or radiographically stable disease (SD, MR, PR or CR) but have experienced a reversible treatment-emergent adverse event, the dose of study drug can be delayed for up to 14 days after the scheduled dosing date. A subject for whom dosing is delayed > 14 days should be discontinued from the study.
- During any cycle, if a subject develops an ANC < 500/μL, platelets < 10,000/μL, or a hemoglobin < 6.5 g/dL, blood samples must be collected every 3 days and study treatment withheld. Treatment may resume when ANC returns to ≥ 1,000/μL, platelet counts return to ≥ 50,000/μL or baseline platelet count levels (in subjects with baseline platelets < 50,000/μL), or hemoglobin returns to ≥ 8.0 g/dL.
- AMG 340 should be discontinued in any subject who experiences CRS, TLS, or a non-hematologic treatment-emergent adverse event that meets DLT equivalent criteria until resolution of the toxicity to ≤ grade 1 or baseline; thereafter study drug may be resumed with one dose level reduction with Medical Monitor approval.

Up to 2 dose reductions are allowed to manage toxicity; thereafter toxicity will be deemed 'unacceptable' and the subject will be discontinued from therapy. Assessment schedules and cycles are fixed and should continue regardless of whether a dose is held.

While investigator discretion should be used for subject management with regards to toxicities, guidelines for management of CRS and NT are provided in Table 6-6 and Table 6-5.

6.2.1.4.1 Dose Limiting Toxicity Definition for Dose Escalation

The DLT observation period for dose escalation purposes is 21 days and covers the first complete treatment cycle of AMG 340 (1 dose of AMG 340; or up to 3 doses if priming has been implemented). Regular teleconferences will be conducted among the DLRT to examine/confirm potential DLTs, assess adverse events, and evaluate laboratory abnormalities. Events occurring outside the DLT window may be evaluated during these calls when making dose escalation decisions. A DLT is defined as a treatment emergent adverse event that is not unequivocally due to the subject's underlying malignancy or other extraneous cause and meets the criteria below.

The NCI-CTCAE version 5.0 will be used. DLT definitions are provided below.

6.2.1.4.1.1 Non-hematologic Dose-limiting Toxicity

- Non-hematological adverse events grade ≥ 3 with the following exceptions:
  - Grade 3 or 4 isolated electrolyte abnormalities (ie, those occurring without clinical consequence) that resolve, with or without intervention, to grade ≤ 1 within 72 hours.
  - Grade 3 hyperglycemia responsive to optimal medical management within 72 hours.
  - Grade 3 nausea/vomiting/diarrhea responsive to optimal medical management within 72 hours.
  - Alopecia or vitiligo of any grade.
  - Grade 3 fatigue lasting < 10 days.
  - Grade 3 fever (defined as a temperature ≥ 40°C with a duration of ≤ 24 hours occurring outside the context of CRS
  - Laboratory parameters of grade 3, not considered clinically relevant, and improved to grade (less than or equal to) 2 within 72 hours, will not be considered DLTs. Laboratory parameters with long half-lives, (ie, ALT, GGT, ALP, and lipase), will likewise not be considered DLTs if they are not considered clinically relevant, and improve to grade ≤ 2 within 7 days.
  - Adverse events that require a delay in initiation of the next scheduled cycle by > 14 days.

6.2.1.4.1.2 Hematologic Dose-limiting Toxicity

- Grade 3 CRS that does not resolve to ≤ grade 1 within 72 hours or grade 4 CRS.
- Grade 3 TLS that does not resolve to ≤ grade 1 within 72 hours or grade 4 TLS.
- Grade 4 neutropenia for > 5 days or febrile neutropenia.
- Grade 3 thrombocytopenia with bleeding or grade 4 thrombocytopenia.
- Grade 4 anemia.
- Grade 5 adverse events.
- Lymphopenia will not be considered a DLT.

- Adverse events that require a delay in initiation of the next scheduled cycle by > 14 days.

6.2.1.5 Echocardiogram/Multigated Acquisition Scan

Echocardiogram (ECHO) or multigated acquisition (MUGA) will be performed to assess cardiac ejection fraction and will occur at time points specified in the Schedule of Activities (Section 1.3).

ECHO/MUGA should include an evaluation from left ventricular ejection fraction. Additional ECHO/MUGA assessments may be performed as clinically indicated.

6.2.1.6 Specific Guidance for Cytokine Release Syndrome

Refer to Appendix 10 **(Section** 11.10**)** for CRS definitions.

The symptoms associated with the CRS event do not meet the definition of an adverse event as defined in Section 11.4. Therefore, the CRS associated event (ie, CRS, cytokine storm) should be documented on the Event CRF as the diagnosis. However, since it is important to document all symptoms related to a CRS event, a CRS Symptoms eCRF will also be available to record the symptoms associated with each CRS event. If the severity of a CRS event changes from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF and fill out an associated CRS Symptoms eCRF. If the symptoms worsen enough to impact the overall CRS grade, it is important to remember to record a new CRS event on the Event eCRF with the appropriate grade. Temperature may normalize within a few hours of treatment, whereas the other components of CRS take longer to resolve. Once treatments are used to manage the fever, the subject is considered to still have CRS, even in the absence of fever, until all signs and symptoms leading to the diagnosis of CRS have resolved. Likewise, CRS can be downgraded in an afebrile subject treated with anti-cytokine therapy as their hemodynamic status and/or hypoxia improves. Typically, a subject with severe CRS whose fever, oxygen, and pressor requirements have resolved may be assumed to have resolved CRS unless there are alternative causes for the fever, hypoxia, and/or hypotension.

Table 6-2. CRS Grading (ASTCT; Lee et al, 2019)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C

		With		
Hypotension	None	Not requiring vasopressors	Requiring a single vasopressor (not including vasopressin)	Requiring multiple vasopressors (not including vasopressin)
		And/or[b]		
Hypoxia	None	Requiring low-flow oxygen (≤ 6 L/minute) nasal cannula or blow-by	Requiring high-flow nasal cannula (> 6 L/min), facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome
Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[b] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

6.2.1.6.1.1 Neurological Dose-limiting Toxicity

The etiology of NT is unclear but has been postulated to stem from endothelial activation/microangiopathy, possibly downstream of IL-1 secretion by monocytes/macrophages (Gust et al, 2017; Giavidris et al, 2018; Norelli et al, 2018). Onset usually occurs with or after CRS (mostly CRS grade ≥ 3). Isolated NT has been described after administration of anti-PSMA T-BsAbs (Velasquez et al, 2017). Early symptoms of NT include tremor, dysgraphia, expressive aphasia, impaired attention, and lethargy; delirium, headache, agitation, cerebral edema, ataxia, confusion, seizure, and coma may subsequently develop.

If NT symptoms are suspected, grading should be performed to guide appropriate management; a consensus grading scheme published by Lee and colleagues is reproduced here and may be used to grade NT (Table 6-3; Lee et al, 2019).

Table 6-3. American Society for Transplantation and Cellular Therapy Immune Effector Cell-associated Neurotoxicity Syndrome Consensus Grading for Adults (Lee et al, 2019)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7–9	3–6	0–2	0 (subject is unarousable and unable to perform ICE)

Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Subject is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
Seizure	NA	NA	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	NA	NA	NA	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	NA	NA	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve 6th palsy; or papilledema; or Cushing's triad

EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; NA = not applicable.
Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a subject with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
[a] A subject with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.
[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
Source: Lee et al, 2019

Neurological adverse events in subjects receiving AMG 340 mandate frequent CAR-T-cell therapy associated toxicity (CARTOX-10) or immune effector cell encephalopathy (ICE) examinations (Table 6-4) and neurological exams. Early neurology consultation, use of anti-epileptics, and intensive care unit/airway support as needed are encouraged. Table 6-5 provides a guideline for treatment that may be used for subject management, however, it is recommended that investigators adhere to institutional guidelines for NT management, if they exist.

Table 6-4. Encephalopathy Assessment Tools for Grading of Immune Effector Cell-associated Neurotoxicity Syndrome (Lee et al, 2019)

CARTOX-10	ICE
• Orientation: orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points	• Orientation: orientation to year, month, city, hospital: 4 points • Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
• Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points	• Following commands: ability to follow simply commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• Writing: ability to write a standard sentence (eg, Our national bird is the bald eagle"): 1 point	• Writing: ability to write a standard sentence (eg, Our national bird is the bald eagle"): 1 point
• Attention: ability to count backwards from 100 by 10: 1 point	• Attention: ability to count backwards from 100 by 10: 1 point

CARTOX-10 = chimeric antigen receptor toxicity; ICE = immune effector cell encephalopathy.
Note: CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
Note: Scoring: 10, no impairment; 7-9, grade 1 ICANS; 3-6, grade 2 ICANS; 0-2, grade 3 ICANS; 0 due to subject unarousable and unable to perform ICE assessment, grade 4 ICANS.
Source: Lee et al, 2019

Table 6-5. Suggested Guidelines for Management of Neurological Toxicity

Adverse Event Category	Guidelines
Neurologic adverse event after dosing with AMG 340	• Consult neurologist • Continue neurologic monitoring • Prophylactic anti-epileptic (ie, levetiracetam) • Consider MRI/CT, EEG, and/or LP • Contact Medical Monitor
If adverse event is grade ≥ 2, add	• Consider Corticosteroids (eg, dexamethasone 10 to 20 mg IV every 12 to 24 hours, higher doses or with more frequency, if clinically indicated) • Withhold AMG 340 until resolution to grade ≤ 1.
If adverse event is grade ≥ 3, add	• High-dose corticosteroids (methylprednisolone 2 mg/kg loading dose followed by 2 mg/kg/day divided 4 times per day). Higher /more frequent doses if indicated. Taper when grade 1 or better) • Anti-epileptics for seizures/seizure-like activity • ICU monitoring • Airway protection • Consider continuous EEG monitoring
If adverse event is grade 4, add	• If cerebral edema/other grade 4 toxicity is rapid onset or the subjects is unresponsive to above: methylprednisolone IV 1 g/day x 3 days, followed if clinically indicated by taper. • Consider hyperventilation / hyperosmolar therapy for cerebral edema.

CT = computed tomography; EEG = electroencephalogram; ICU = intensive care unit; IV = intravenous; LP = lumbar puncture; MRI = magnetic resonance imaging

6.2.1.6.1.2 Miscellaneous Dose-limiting Toxicity

Any toxicity thought to be related to the study drug that, at the discretion of the investigator, is thought to warrant withholding the drug. Other adverse events may be considered a DLT as determined by the Medical Monitor, in conjunction with the investigator.

All decisions regarding continued dosing for individual subjects will be medically managed by the investigator, in conjunction with the Medical Monitor(s), as appropriate. These decisions will be driven by the DLT criteria as described above.

Any subject who does not complete the full 21-day DLT observation period for any reason other than DLT will be considered non-DLT-evaluable for dose escalation and/or MTD assessment and will be replaced at the same dose level. Additional subjects may be enrolled at a given dose level in the absence of DLT to explore factors influencing adverse events or to accumulate additional safety data.

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

6.2.2.1 Amgen Investigational Product: AMG 340

The reason for dose change of AMG 340 is to be recorded on each subject's CRF(s).

Subjects experiencing CRS must continue to be hospitalized as described in Table 6-6 and as deemed appropriate by the investigator. Subjects should be monitored for CRS symptoms, including vital signs and pulse oximetry at least every 2 hours for 12 hours, or until CRS grade ≤ 1, whichever is earlier.

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. Dexamethasone premedication is mandatory prior to re start, and prior to re-escalation to the target dose in case of dose reduction. The following assessments should be performed as per the Schedule of Activities for cycle 1, depending on duration of hospitalization:

- vital signs, pulse oximetry
- physical examination
- neurological examination (only in case the treatment interruption was due to a neurologic event)
- weight
- ECOG
- safety labs (hematology, chemistry, coagulation, urinalysis)

The subject should be hospitalized for up to 48 hours after re-start of the infusion depending on the specific adverse event that has led to the interruption/delay (causality and severity, see Table 6-6 for adverse event management and restart guidance) or tolerability prior to delay for logistical reason and as per agreement with the Amgen Medical Monitor. **Re-introduction of the step dosing may be required for long delays and should be considered on a case-by-case basis with the Amgen Medical Monitor.**

6.2.2.2 Management of COVID-19 Infection

Subjects with evidence of COVID-19 infection should be closely monitored while being treated with AMG 340. Follow the guidelines in Table 6-6 for AMG 340 treatment interruption, resumption, and discontinuation due to COVID-19 infection. Subjects with active COVID-19 infection should not be dosed with AMG 340 until infection has resolved and if being treated with an anti-infective therapy, the course of such therapy should have been completed. Management of COVID-19 infection should be tailored to the appropriate prophylaxis and/or treatment according to the local standard of care and institutional guidelines.

6.2.2.3 Management of Monkeypox Infection

Subjects with evidence of Monkeypox infection should be closely monitored while being treated with AMG 340. Follow the guidelines in Table 6-6 for AMG 340 treatment interruption, resumption, and discontinuation due to Monkeypox infection. Management of Monkeypox infection should be tailored to the appropriate prophylaxis and/or treatment for the Monkeypox infection according to the local standard of care and institutional guidelines.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity	Interruption/Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Infusion-related Reaction					
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated	**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**
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Short-term infusion: Immediate interruption/delay until event has improved to grade ≤ 1		• Re-start possible, if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • Delay of the next infusion: – ≤ 7 days: administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: skip the delayed 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	If subject missed more than 2 consecutive doses of AMG 340

Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity	Interruption/Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Infusion-related Reaction (continued)					
3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	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 of AMG 340
4	Life-threatening consequences; urgent intervention indicated	**N/A**	As for grade 3 infusion-related reaction	**N/A**	Immediately stop the infusion (if applicable) and permanently discontinue AMG 340 (monotherapy or in combination with pembrolizumab) therapy

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity	Interruption/ Delay	Specific Management	Re-start guidance	Permanent Discontinuation
Neurologic Events					
≤ 2	For CRS-related neurological events, use ICANS grading and management system (Section 6.2.1.6.1.1)	Interrupt AMG 340 until the event improves to grade ≤ 1	Follow institutional guidelines for management	Resume AMG 340 no less than 72 hours after the initial observation of the grade 1 or 2 adverse event.	**N/A**
3			Administer corticosteroids per local practice	Resume AMG 340 no less than 7 days after the initial observation of the grade 3 adverse event. Reduce AMG 340 by 1 dose level.	• Initial grade 3 neurologic event does not improve to grade ≤ 1 within 7 days, OR • Grade 3 neurologic event reoccurs at the lower dose level within 7 days of re-initiation
4		--	--	--	Permanently discontinue AMG 340
Seizure		Interrupt AMG 340 until the event improves to grade ≤ 1	Administer corticosteroids and anti-seizure medication per local practice	• Refer to grade 3 neurologic events above for dose level rules for re-instituting infusion. • Do not re-initiate AMG 340 until 7 days after the last seizure and after therapeutic levels of anti-seizure medication are likely to have been achieved.	If a second seizure occurs with re-initiation of AMG 340 at any dose

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome (see Section 6.2.1.6 for additional guidance and grading scale details)					
1	Symptoms are not life-threatening and require symptomatic treatment only • Fever[b]: ≥ 38°C • Hypotension: none • Hypoxia: none	No action required	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Consider Chest X-Ray and obtaining appropriate cultures to rule out infection For subjects with rapid onset (< 4 hours from start of infusion), extensive co-morbidities or poor performance status, strong suggestion to manage per grade 3 CRS guidance below. Thrombocytopenia occurring in the setting of CRS can be managed per Section 6.2.1.4 and/or per institutional guidelines.	**N/A**	**N/A**

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 6.2.1.6 for additional guidance and grading scale details)					
2	Symptoms require and respond to moderate intervention • Fever[b]: ≥ 38°C WITH • Hypotension: not requiring vasopressors AND/OR[c] • Hypoxia: requiring low-flow nasal cannula[d] or blow-by	Delay AMG 340 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 (low-flow [≤ 6 L/minute] nasal cannula or blow-by) • IVF when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg, > 120 bpm) may also indicate the need for intervention for hypotension. Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Cardiac and other organ function • Consider Chest X-Ray and obtaining appropriate cultures to rule out infection For subjects with rapid onset (< 4 hours from start of infusion), extensive co-morbidities or poor performance status, strong suggestion to manage per grade 3 CRS guidance below. Thrombocytopenia occurring in the setting of CRS can be managed per Section 6.2.1.4 and/or per institutional guidelines.	• The next infusion may be administered if all of the following criteria are met: – If CRS occurred during AMG 340 infusion, infusion has been interrupted for at least 72 hours – Resume AMG 340 at same dose or reduce to next lower dose if clinically indicated. – The event has resolved to grade ≤ 1 prior to restarting treatment	If there is no improvement to CRS ≤ grade 1 within 7 days

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 6.2.1.6 for additional guidance and grading scale details)					
3	Symptoms require and respond to aggressive intervention • Fever[b]: ≥ 38°C WITH • Hypotension: requiring a single vasopressor (excluding vasopressin) AND/OR[c] • Hypoxia: requiring high-flow nasal cannula[d], facemask, nonrebreather mask, or Venturi mask	Delay AMG 340 until event improves to CRS grade ≤ 1.	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever • Supplemental oxygen (high-flow nasal cannula [> 6 L/min], facemask, non-rebreather mask, or Venturi mask), as needed • A vasopressor ± vasopressin, as needed • Dexamethasone (or equivalent) IV at a dose maximum of (3 doses of 8 mg [24 mg/d]). The dose should then be reduced step-wise. AND/OR • Consider use of tocilizumab (in countries where available) as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose. Tocilizumab can be repeated for an additional 3 doses with at least an 8 hour interval between doses	• The next 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 340 infusion, infusion has been interrupted for at least 72 hours – The event has resolved to grade ≤ 1 prior to re-starting treatment	If there is no improvement to CRS ≤ grade 2 within 5 days and CRS ≤ grade 1 within 7 days. In the case of 2 separate grade 3 CRS events.

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 6.2.1.6 for additional guidance and grading scale details)					
			• If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of CRS. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (SYLVANT® Prescribing Information, 2019), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of AMG 340. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab. Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Consider Chest X-Ray and obtaining appropriate cultures to rule out infection • If refractory hypotension (after 2 fluid boluses), consider ECHO Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Thrombocytopenia occurring in the setting of CRS can be managed per Section 6.2.1.4 and/or per institutional guidelines.		

Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 6.2.1.6 for additional guidance and grading scale details)					
4	Life-threatening symptoms • Fever[b]: ≥ 38°C WITH • Hypotension: requiring multiple vasopressors (excluding vasopressin) AND/OR[c] • Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	**N/A**	Administer: • Symptomatic treatment (eg, paracetamol/acetaminophen) for fever • Supplemental oxygen (positive pressure [eg, CPAP, BiPAP, intubation and mechanical ventilation]), as needed • Multiple vasopressors, as needed • Dexamethasone (or equivalent) IV at a dose maximum of (3 doses of 8 mg [24 mg/d]). Further corticosteroid use should be discussed with the Amgen medical monitor. • Tocilizumab should be administered at a dose of 4-8 mg/kg as a single dose. Tocilizumab can be repeated for an additional 3 doses with at least an 8 hour interval between doses	**N/A**	Immediately stop the infusion (if applicable) and permanently discontinue AMG 340

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Cytokine Release Syndrome continued (see Section 6.2.1.6 for additional guidance and grading scale details)					
			• If tocilizumab is not available, siltuximab (an anti-IL-6 monoclonal antibody) may be used in the management of CRS, following the criteria outlined in the Management of Adverse Events table. The recommended dose of siltuximab is 11 mg/kg administered over 1 hour as an intravenous infusion, consistent with the prescribing information for the treatment of multicentric Castleman's disease (SYLVANT® Prescribing Information, 2019), and the CARTOX Working Group Guidelines for CRS management (Neelapu, 2018). Siltuximab may be repeated if needed, in the event that CRS recurs after a subsequent infusion of AMG 340. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab. Monitor: • CRS symptoms including temperature, blood pressure, and pulse oximetry • Fluid status, maintain IVF as needed • Consider Chest X-Ray and obtaining appropriate cultures to rule out infection • If refractory hypotension (after 2 fluid boluses), consider ECHO Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Thrombocytopenia occurring in the setting of CRS can be managed per Section 6.2.1.4 and/or per institutional guidelines.		

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Description of Severity[a]	Interruption/ Delay	Specific Management	Restart Guidance	Permanent Discontinuation
Tumor Lysis Syndrome (TLS) – Grading according to Cairo-Bishop Criteria (see Section 11.11)					
2	• Clinical TLS	Immediate interruption/ delay until event has improved to grade ≤ 1	TLS should be managed according to the local standard of care and institutional guidelines.	• Restart 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. • Delay of next infusion: - ≤ 72 hours: follow the Schedule of Activities 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 Activities for the next scheduled infusion • Hospitalization: 40 to 48 hours	**N/A**
≥ 3	• Clinical TLS	N/A	TLS should be managed according to the local standard of care and institutional guidelines	**N/A**	Immediately stop the infusion (if applicable) and permanently discontinue AMG 340 therapy

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Interruption/ Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Gastrointestinal events related to AMG 340				
2	Interruption/delay required if deemed intolerable by the subject or investigator and not responding to appropriate medical management until event has improved to grade ≤ 1	Gastrointestinal (GI) toxicities should be managed according to the local standard of care and institutional guidelines	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • Delay of next infusion: – ≤ 7 days: Administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: Skip the delayed 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	If subject missed more than 2 consecutive doses of AMG 340

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Interruption/ Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Gastrointestinal events related to AMG 340 (continued)				
≥ 3	Interruption/delay until event has improved to grade ≤ 1	Gastrointestinal (GI) toxicities should be managed according to the local standard of care and institutional guidelines	• Re-start possible if successfully managed and improvement to ≤ grade 1 in ≤ 14 days. • Delay of next infusion: – ≤ 7 days: Administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: Skip the delayed 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	If subject missed more than 2 consecutive doses of AMG 340 OR In case of reappearance of same event at grade 4 OR In case of repeat grade ≥ 3 event despite dose reduction

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Interruption/Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Any other AMG 340-related events not meeting DLT criteria				
≥ 3	Interruption/delay required if deemed intolerable and/or clinically significant by the subject or investigator 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. • Delay of next infusion: – ≤ 7 days: Administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: Skip the delayed 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	If subject missed more than 2 consecutive doses of AMG 340 OR In case of reappearance of same event at grade 4 OR In case of repeat grade ≥ 3 event despite dose reduction

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Grade	Interruption/Delay	Specific Management	Re-start Guidance	Permanent Discontinuation
Any Non-AMG 340-related events				
4	Interruption/ delay required if deemed intolerable by the subject or investigator 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 ≤ 28 days. • Delay of next infusion: – ≤ 7 days: Administer the delayed infusion (as long as the next scheduled infusion is > 6 days from delayed infusion) and follow the schedule of assessments for the cycle day on which the infusion was originally planned. – > 7 days: Skip the delayed 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	If subject missed more than 2 consecutive doses of AMG 340 OR In case of reappearance of same event at grade 4

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Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

Pituitary Gland Dysfunction (González-Rodríguez and Rodríguez-Abreu, 2016; Brahmer et al, 2018)
• Monitor for signs and symptoms of pituitary gland dysfunction, TSH, FT4, cortisol, and ACTH throughout study (prolactin, FSH, LH, testosterone/estradiol only at baseline and EOT) – Abnormal hormone monitoring result or clinical suspicion of pituitary gland dysfunction (headache, fatigue, asthenia, impaired vision, vomiting, hypotension, amenorrhea, impotence) – Diagnostic tests: Consider brain MRI (if clinically indicated) with or without contrast with pituitary/sellar cuts in subjects with multiple endocrine abnormalities and/or with new headache or vision changes. Evaluate ACTH, AM Cortisol, TSH, FT4, electrolytes and consider evaluating LH, FSH, and testosterone levels in males or estrogen in females. • Obtain endocrinology consultation for hypophysitis or if clinically indicated • Once pituitary gland dysfunction is confirmed, hold further treatment with AMG 340 pending completion of evaluation. Manage pituitary dysfunction according to NCCN or ASCO guidelines for Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (NCCN Guidelines, 2022; Brahmer et al, 2018). • Once stabilized on any replacement hormones and taking 10 mg or less of prednisone or equivalent may consider restarting AMG 340. If subject experienced grade 3 or higher pituitary dysfunction, must discuss with medical monitor prior to restarting treatment. • Continue endocrinological surveillance
Hepatotoxicity
For Stopping and Rechallenge Rules please refer to Section 11.7.

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Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

CTCAE Grade[e]	Interruption/ Delay[f]	Specific Management	Re-start Guidance[f]	Permanent Discontinuation[f]
Monkeypox Infection				
Grade 1: **Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated**	**Interruption is not required unless the subject must be isolated for the event per local standard of care and institutional guidelines taking into consideration the benefit/risk of withholding treatment**	**Follow local guidelines and standard of care for Monkeypox treatment and isolation, if applicable.**	**If interruption is required:** • **Resolution of Monkeypox infection** • **Resume at the same dose**	**None**
Grade 2: **Moderate symptoms: minimal, non-invasive intervention indicated; limited age-appropriate instrumental ADL[g]**	**Interruption required until the event resolves**	**Follow local guidelines and standard of care for Monkeypox treatment and isolation, if applicable.**	• **Resolution of Monkeypox infection** • **Resume at the same dose**	**None**

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Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

CTCAE Grade[e]	Interruption/ Delay[f]	Specific Management	Re-start Guidance[f]	Permanent Discontinuation[f]
Monkeypox Infection				
Grade 3: **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limited selfcare ADL[h]**	**Interruption required until the event resolves**	**Follow local guidelines and standard of care for Monkeypox treatment and isolation, if applicable.**	• **Resolution of Monkeypox infection** • **Resume at the same dose or lower dose as clinically indicated**	**Permanently discontinue investigational product therapy, if a subject required treatment interruption greater than 28 days due to grade 3 infection considering the individual benefit/risk**
Grade 4: **Life-threatening; consequences; urgent intervention indicated**	**Interruption required until the event resolves**	**Follow local guidelines and standard of care for Monkeypox treatment and isolation, if applicable.**	• **Resolution of Monkeypox infection** • **Reduce to next lower dose**	**Permanently discontinue investigational product therapy, if a subject required treatment interruption greater than 28 days due to grade 4 Monkeypox infection considering the individual benefit/risk**

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Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

CTCAE Grade[e]	Interruption/Delay	Specific Management	Restart Guidance[f]	Permanent Discontinuation[f]
SARS-CoV-2 infection and COVID-19 disease				
Grade 1: **Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated**	Interruption required until at least **5** days[i] since positive SARS-COV-2 test **or since resolution of acute symptoms.**	Follow local guidelines and **standard of care** for COVID-19 treatment and isolation	• **Resolution of the acute symptoms** • Subject tests negative for SARS-COV-2**,** ○ If subject continues to test positive for SARS-COV-2 more than **5** days[i] after initial positive test or **after resolution of symptoms,** resume **investigational product** only after discussion with subject and reassessment of individual risk/benefit • **Resume at the same dose**	**None**
Grade 2: **Moderate symptoms: minimal, non-invasive intervention indicated; limited age-appropriate instrumental ADL**	**Interruption required until at least 5 days[i] since resolution of acute symptoms**	**Follow local guidelines and standard of care for COVID-19 treatment and isolation**	• **Resolution of the acute symptoms** • **Subject tests negative for SARS-COV-2,** ○ **If subject continues to test positive for SARS-COV-2 more than 5 days[i] after resolution of symptoms, resume investigational product only after discussion with subject and reassessment of individual risk/benefit** • **Resume at the same dose**	**None**

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Abbreviations and footnotes defined on last page of table.

Table 6-6. AMG 340 Dose Modification Guidelines for Adverse Events

CTCAE Grade[e]	Interruption/Delay	Specific Management	Restart Guidance[f]	Permanent Discontinuation[f]
SARS-CoV-2 infection and COVID-19 disease				
Grade 3: **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limited self-care ADL**	**Interruption required until at least 10 days since resolution of acute symptoms**	**Follow local guidelines and standard of care for COVID-19 treatment and isolation**	• **Resolution of the acute symptoms** • **Subject tests negative for SARS-COV-2** ○ **If subject continues to test positive for SARS-COV-2 more than 10 days after resolution of symptoms, resume investigational product only after discussion with subject and reassessment of individual risk/benefit** • **Resume at the same dose or reduce to next lower dose if clinically indicated**	**Permanently discontinue investigational product therapy if subject required treatment interruption greater than 28 days due to grade 3 COVID-19 infection**
Grade 4: **Life-threatening; consequences; urgent intervention indicated**	**Interruption required until at least 10 days since resolution of acute symptoms**	**Follow local guidelines and standard of care for COVID-19 treatment and isolation**	• **Resolution of the acute symptoms** • **Subject tests negative for SARS-COV-2** ○ **If subject continues to test positive for SARS-COV-2 more than 10 days after resolution of symptoms, resume investigational product only after discussion with subject and reassessment of individual risk/benefit** • **Resume at the same dose or reduce to next lower dose if clinically indicated**	**Permanently discontinue investigational product therapy if subject required treatment interruption greater than 28 days due to grade 4 COVID-19 infection**

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ACTH = adrenocorticotropic hormone; ASCO = American Society of Clinical Oncology; BiPAP = bilevel positive airway pressure; CRS = cytokine release syndrome; COVID-19 = coronavirus disease 2019; CPAP = continuous positive airway pressure; CT = computed tomography; **CTCAE = Common Terminology Criteria for Adverse Events;** DLT = dose-limiting toxicity; ECG = electrocardiogram; ECHO = echocardiogram; EOT = end of treatment; FSH = follicle stimulating hormone; FT4 = free t4; ICANS = immune effector cell associated neurologic syndrome; IL6 = interleukin6; IV = intravenous; IVF = intravenous fluid(s); LH = luteinizing hormone; MRI = magnetic resonance imaging; **N/A** = not applicable; NCCN = National Comprehensive Cancer Network; NSAIDs = non-steroidal anti-inflammatory drug(s); RTPCR = real-time polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SOC = standard of care; TLS = tumor lysis syndrome; TSH = thyroid stimulating hormone

[a] American Society for Transplantation and Cellular Therapy (ASTCT) grading system for CRS (Lee et al, 2019).
[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In subjects who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
[c] CRS grade is determined by the more severe event: Hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
[d] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute.
[e] Document severity of COVID-19 or Monkeypox related adverse events utilizing the "Infection and Infestations – Other, specify" category per CTCAE version 5.0 as specified in the clinical protocol.
[f] Amgen Medical Monitor to decide based on investigational product safety risk and patient population whether to allow a subject who demonstrates a clinical benefit with a documented response of stable disease or better to resume therapy if there are reasons that the above dose withholding and restarting rules cannot be implemented. The investigator should contact and discuss these reasons with Amgen Medical Monitor. The investigator must obtain written agreement from Amgen Medical Monitor before any changes in the dose modification rules can be implemented.
[g] Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[h] Selfcare ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
[i] Amgen Medical Monitor to decide if investigational product should be interrupted for 10 days for grade 1 or grade 2 COVID-19 adverse event, based on investigational product safety risk and patient population.

6.2.2.4 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 IV infusion administration of AMG 340 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 of ≤ 2 hours, the IV infusion administration can be restarted. In case of infusion interruption of > 2 hours, immediately consult with Amgen Medical Monitor to determine if:

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

For short-term (120 minutes) infusions, 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 Activities (Section 1.3) or the cycle day on which the original (interrupted) infusion was administered. Premedication as described in Section 6.1.5 for treatment cycle 1 should be administered.

Any interruption of an infusion should be recorded in the eCRF, providing the start and stop date/time of the infusion if the interruption is > 2 hours.

Infusion Delay due to Technical/Logistical Issues

If the infusion delay was ≤ 7 days, the dose can be administered without specific precautions. Procedures performed will follow the schedule of assessments for the cycle day on which the infusion was originally planned. The following infusion should then be administered after 21 (± 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 21 days later [± 1 day]). The ± 1-day window is allowed until the original dosing schedule is met again.

6.2.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 11.7 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

6.3 Preparation/Handling/Storage/Accountability

Guidance and information on drug accountability for the investigational product and other protocol-required therapies will be provided to the site.

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Method of Treatment Assignment

Subjects who meet eligibility criteria and enroll in the study will be assigned to treatment with AMG 340.

6.4.2 Blinding

This is an open-label study; procedures to blind treatment assignment are not applicable.

6.5 Treatment Compliance

When subjects are dosed at the site, they will receive AMG 340 directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

6.6 Treatment of Overdose

The administered AMG 340 monotherapy 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 required for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdosage. Consultation with the Amgen medical monitor is also required 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 11.4.

A dose of > 10% higher than the intended AMG 340 dose will be considered clinically important and classified as a serious adverse event under the criterion of “other medically important serious event” per Section 11.4.

6.7 Prior and Concomitant Treatment

6.7.1 Prior Treatment

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded from 2 weeks (14 days) prior to dosing.

Additionally, all prior cancer treatment therapies will be collected. Other prior therapies that were being taken/used from 1 month prior to signing informed consent will be collected. For all prior therapies not taken for prostate cancer, collect therapy name, indication, dose, unit, frequency, route, and start and stop dates.

For all prior therapies taken for prostate cancer (eg, chemotherapy, immunotherapy, biological therapy, or targeted therapy), collect (in the order they were administered):

- therapy name
- indication
- dose and schedule of the agent(s)
- unit
- frequency
- start and stop dates
- disease state in which it was administered
- reason for discontinuation (disease progression, clinical progression, toxicity, subject's decision)

Additionally, details of the dates, portals, and total administered dose by portal should be recorded for all courses of radiation therapy, including those directed at the primary and metastatic site(s).

6.7.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.1.7.

Concomitant therapies are to be collected from informed consent through the end of SFU period.

For concomitant therapies being taken for the disease under study (eg, steroids, chemotherapy on oncology studies), collect therapy name, dose, unit, frequency, start date, and stop date. For all other concomitant therapies including vaccines**,** collect therapy name, indication, dose, unit, frequency, route, start date**, and stop date**.

6.7.2.1 Vaccines

Every effort should be made to **fully vaccinate patients** prior to 14 days from first dose of **investigational product. However,** SARS-COV-2 vaccinations **should be avoided** during screening (within a minimum of 14 days from first dose of **investigational product) and should be also avoided** in the first treatment cycle for better assessment of safety parameters. Throughout the **trial,** SARS-COV**-**2 vaccination should be avoided within **7** days after the administration of **investigational product.** In the event where a **patient** requires steroids **or other immunosuppressive therapy for** treatment of adverse events, vaccination should be avoided while on steroids **or other immunosuppressive therapy.**

The following vaccines (Live and live-attenuated vaccines) are excluded during the following study periods:

- **Screening and during study treatment: Live and live-attenuated vaccines are prohibited within 28 days prior to the first dose of investigational product and for the duration of the study.**
    - **Live viral non-replicating vaccine (eg, Jynneos) for Monkeypox infection is allowed during the study in accordance with local standard of care and institutional guidelines, but is restricted within 7 days prior to first dose of investigational product and during the DLT assessment period.**
- **End of study treatment: Live and live-attenuated vaccines can be used at least 5X half-life of investigational product after the last dose of investigational product.**

7. Discontinuation of Study Treatment and Subject Discontinuation/Withdrawal

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Section 7.1.

7.1 Discontinuation of Study Treatment

Subjects (or a legally authorized representative) can decline to continue receiving investigational product and/or other protocol-required therapies and/or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 1.3) 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, and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies and/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.

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

- decision by sponsor
- lost to follow-up
- death
- adverse event
- noncompliance with protocol
- subject request
- disease progression (refer to Appendix 12 **[Section** 11.12**]**)
- requirement for alternative therapy
- protocol-specified criteria including:
  - intercurrent illness preventing further drug administration
  - treatment delay > 14 days, unless the cause is unequivocally due to the subject's underlying disease or other extraneous cause and continuation is approved by the Medical Monitor(s) and treating investigator.

7.2 Subject Discontinuation/Withdrawal From the Study

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

can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records. Subjects who are withdrawn or removed from treatment or the study will not be replaced unless they are not evaluable for DLT in cycle 1.

If a subject discontinues study drug treatment, an EOT visit should be conducted within 30 days after the last dose of AMG 340, as well as a 90-day follow-up visit if possible, provided the subject has not initiated a new line of therapy. Subjects with grade 3 or 4 drug associated toxicities through the 90-day follow-up visit will be followed until the subject is stable, toxicities resolve to an acceptable level, or until another anticancer therapy is initiated, whichever occurs earlier.

If a subject withdraws or is discontinued from the study, the reason(s) for discontinuation from the study will be recorded if known, and an EOT visit (and associated procedures) will be performed within 30 days after the last dose of study drug. Additional blood samples for drug measurement may be collected from subjects who are discontinued due to adverse events. Subjects will be asked to return, if possible, for a 90-day (+ 7 days) follow-up visit after the last dose of AMG 340. However, if subjects start a new line of therapy before the 90 (+ 7) days follow-up visit, subjects will be asked to return for a SFU visit approximately 30 days after the last dose of AMG 340 or until the subject begins a new line of therapy, whichever occurs later. Once reliable half-life data are available for AMG 340 and if $T_{1/2}$ exceeds 18 days, subjects may be asked to return at a time more remote from the last dose of AMG 340 for a SFU visit to capture PK and ADA data at $T \geq 5 \times T_{1/2}$.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 11.6 for further details). Refer to the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.2.1 Reasons for Removal From Washout Period, Run-in Period, or Invasive Procedures

Not applicable for this study.

7.2.2 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

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator should search publicly available records [where permitted] to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

8. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Section 1.3).

If an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1 General Study Periods

8.1.1 Screening, Enrollment, and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen

the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 5.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 28 days after the original signing of the informed consent form, all screening procedures (with the exception of tumor biopsy, PSMA PET and FDG PET scans), including informed consent, must be repeated.

8.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 1.3). On-study visits may be completed within the deviation window presented in the Schedule of Activities (Section 1.3). The date of the first dose of AMG 340 is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of AMG 340 is to be administered last during each visit that it is required.

8.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a SFU visit will be performed approximately 90 (+ 7) days after the end of the last dose of investigational product and/or protocol-required therapies. However, if subjects start a new line of therapy before the 90 (+ 7) days follow-up visit, safety follow-up will be performed through 30 days post last dose of investigational product or until the subject begins a new line of therapy, whichever occurs later. All procedures to be completed during safety follow-up are indicated in the Schedule of Activities (Section 1.3).

8.1.4 Long-term/Survival Follow-up

Subjects will be followed for survival and/or the commencement of subsequent cancer therapy via clinic visits, telephone, or chart review call every 6 months from the last SFU

visit for up to a maximum of 3 years. All procedures to be completed during long-term/survival follow-up are indicated in the Schedule of Activities (Section 1.3).

8.1.5 End of Study

A subject is considered to have completed the study if he has completed the study including the last visit/last follow-up as shown in the Schedule of Activities (Section 1.3).

8.2 General Assessments

8.2.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

8.2.2 Demographics

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, as allowed by local regulations. Additionally, demographic data will be used to study the impact on biomarkers variability and pharmacokinetics of AMG 340.

8.2.3 Medical History

The investigator or designee will collect a complete medical, surgical, and disease history through day 1. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, mCRPC history must date back to the original diagnosis. Known prostate cancer mutations (eg, BRCA1, BRCA2) prior to start of treatment should also be recorded. The current toxicity will be collected for each condition that has not resolved.

8.2.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

8.2.4.1 Neurological Examination

If clinically indicated, 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).

The individual performing the neurological examination will characterize the findings as either normal or abnormal. Abnormal findings found predose will be reported on the medical history page of the CRF. Abnormal findings found after the subject is dosed will be reported on the Event page of the CRF.

A more detailed neurological assessment may be performed in subjects at selected sites.

8.2.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes. Body Mass Index should be calculated using the following formula: BMI (kg/m^2) = weight (kg)/[height (cm)/100]^2

A limited, symptom-directed physical examination will be performed at other study visits.

8.2.6 Performance Status

The ECOG performance status will be assessed at timepoints indicated in the Schedule of Activities in Section 1.3. The ECOG performance status is documented using the scoring method in Section 11.8.

8.3 Efficacy Assessments

8.3.1 Radiographic Assessments

Radiographic assessments will be obtained as scheduled in Table 1-3 (Schedule of Disease Assessments) relative to cycle 1 day 1 (± 7 days) irrespective of cycle duration including dose delays and treatment discontinuation.

Radiographic scans taken to confirm disease progression following prior anti-cancer therapy may be used for baseline tumor assessments, provided they were performed within 28 days of enrollment and using the same contrast and modality planned to be used for all subsequent assessments.

Standard radiological assessments per protocol should take place until clinically significant disease progression or deterioration, withdrawal of consent, or start of new anticancer therapy. For subjects with PD continuing on treatment beyond progression, imaging should be continued as per local standard of care and images submitted to central reader. Every assessment must include computed tomography (CT)/magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis, all other known sites of disease, and MRI of the brain if a subject has signs or symptoms suggestive of CNS metastases. The CT/MRI can be obtained earlier if clinical deterioration necessitates an

earlier scan at the discretion of the managing physician. The same scanner, contrast, and modality used at screening should be used for all subsequent assessments.

In the dose expansion phase only [redacted] PET/CT will be performed at baseline to assess PSMA-positive tumor burden, and every 12 weeks for response assessment. To identify PSMA-negative disease burden, ^{18}F-FDG PET/CT will also be performed at baseline, and every 12 weeks for response assessment. All imaging assessments have a ± 7-day window. The use of [redacted] PET/CT and ^{18}F-FDG PET/CT (in some countries/regions for prostate cancer) is investigational.

Tumor burden assessments will be performed based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with PCWG3 modifications (see Appendix 12 **[Section** 11.12**]** for details). Responses (PR and CR) require confirmation by a repeat consecutive CT/MRI assessment no sooner than 4 weeks after the first detection of radiographical response. At the discretion of the investigators, the repeat, consecutive confirmation scan may be delayed until the next scheduled scan to avoid unnecessary procedures or radiation burden. Planar bone scintigraphy (for disease status and disease progression assessment) must be performed using conventional ^{99m}technetium methylene diphosphonate (^{99m}Tc-MDP) radionuclide, or other equivalent ^{99m}Tc-labeled radiotracers. Confirmation of bone disease progression by bone scan should be performed as described (“2+2” rule set in PCWG3 guidelines). Disease progression based on both CT/MRI and bone scans will be used in radiographic progression endpoints (eg, time to radiographic progression and [radiographic progression-free survival] rPFS) evaluation. Soft-tissue progression based on CT/MRI scans will be used in response endpoints (eg, objective response and duration of response [DOR]) evaluation. Treatment beyond tumor progression may be allowed as per PCWG3 guidelines (**Section** 11.12) (Scher et al, 2016). Refer to the imaging manual for details on imaging assessments.

For subjects who agree to the optional biopsy, scans must be performed prior to obtaining a biopsy. Blood samples or tumor biopsy must not be collected until at least 24 hours after a PET/CT scan, or at least 60 hours (or 2.5 days) following a bone scintigraphy scan.

For subjects developing COVID-19 during screening period and following screening imaging assessments, consider repeating chest imaging following resolution. For subjects developing COVID-19 during treatment period, consider whether chest imaging should be performed before resuming investigational

product treatment to rule out COVID-19 pneumonia especially in subjects with pulmonary comorbidities.

8.4 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Section 1.3).

8.4.1 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. 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 most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

8.4.2 Electrocardiograms (ECGs)

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. The ECG must include the following measurements: Heart Rate, QRS, QT, QTc, and PR intervals. The PI or (eg, designated site physician, central reader) 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.

8.4.3 Clinical Laboratory Assessments

Refer to Section 11.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 1.3) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Events CRF. The investigator must determine 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.

All protocol-required laboratory assessments, as defined in Section 11.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 1-1).

8.4.4 Survival Status

Survival 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 deceased, the date and reported cause of death should be obtained.

8.4.5 Other Safety

Left ventricular ejection fraction will be assessed by echocardiography at screening. **For subjects developing COVID-19 during screening period and following screening ECHO assessments, consider repeating ECHO following resolution. For subjects developing COVID-19 during treatment period, consider whether ECHO should be performed before resuming investigational product treatment to rule out COVID-19 myocarditis especially in subjects with cardiac comorbidities.**

8.4.6 Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 11.4.

8.4.6.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

8.4.6.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE and is described in Section 11.4. CRS, which will be graded using the criteria referenced in the publication by Lee et al (2019) (see Section 11.10) and TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 11.11), and ICANS will be using the criteria referenced in the publication by Lee et al (2019) (see Section 6.2.1.6.1.1).

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur from the time of consent through the safety follow-up visit 90 (+ 7) days after the last dose of study drug, are reported using

the Events CRF. For subjects that start a new line of therapy before the 90 (+ 7) day follow-up visit, all adverse events should be collected and reported through 30 days post last dose of investigational product/protocol-required therapies or until the subject begins a new line of therapy, whichever occurs later.

8.4.6.1.2 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 **from the time of** consent through the safety follow-up visit **90 (+ 7) days after the last dose of study drug,** are reported using the Events CRF**. For subjects that start a new line of therapy before the 90 (+ 7) day follow-up visit, all serious adverse events should be collected and reported through 30 days post last dose of investigational product/protocol-required therapies or until the subject begins a new line of therapy, whichever occurs later**.

All serious adverse events will be collected, recorded and reported to the sponsor or designee immediately and no later than 24 hours of the investigator's awareness of the event, as indicated in Section 11.4. The investigator will submit any updated serious adverse event data to the sponsor immediately and no later than 24 hours of it being available.

Since the criteria the CTCAE grading scale differs from the regulatory criteria for serious adverse events, if adverse events correspond to grade 4 CTCAE toxicity grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life-threatening status), it will be left to the investigator's judgment to also report these abnormalities as serious adverse events. For any adverse event that applies to this situation, comprehensive documentation of the event's severity must be recorded in the subject medical records.

8.4.6.1.3 Serious Adverse Events After the Protocol-Required Reporting Period

During the long-term follow-up period if the investigator becomes aware of serious adverse events (regardless of causality) after the protocol-required reporting period (as defined in Section 8.4.6.1.2) is complete, then these serious adverse events will be reported to Amgen. The investigator will report serious adverse events to Amgen immediately and no later than 24 hours following the investigator's awareness of the event on the Events CRF.

There is no requirement to actively monitor study subjects after the study has ended with regards to study subjects treated by the investigator. However, if the investigator becomes aware of serious adverse events suspected to be related to investigational product, then these serious adverse events will be reported to Amgen immediately and no later than 24 hours following the investigator's awareness of the event.

Serious adverse events reported **after the end** of the **study** will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study.

8.4.6.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to inquire introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to about adverse event occurrence.

8.4.6.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 11.4.

All new information for previously reported serious adverse events must be sent to Amgen immediately and no later than 24 hours following awareness 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 Events CRF.

8.4.6.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators. The sponsor holding the relevant Investigational New Drug/Clinical Trial Application for either AMG 340 or [redacted] or ^{18}F-FDG has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of AMG 340 or [redacted] or ^{18}F-FDG, respectively, under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Amgen will prepare a single Development Safety Update Report (DSUR) (also referred to as Annual Safety Report [ASR] in the European Union) for the Amgen Investigational Product. In order to ensure that consolidated safety information for the trial is provided, this single DSUR will also include appropriate information on any other investigational products used in the clinical trial, if applicable.

8.4.6.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

8.4.6.6 Pregnancy and Lactation

Details of all pregnancies in female partners of male subjects will be collected after the start of study treatment and until 6 months after last dose of investigational product/protocol-required therapies.

If a pregnancy is reported, the investigator is to inform Amgen immediately and no later than 24 hours of learning of the pregnancy and is to follow the procedures outlined in Section 11.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy are provided in Section 11.5.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

8.5 Pharmacokinetic Assessments

Blood samples will be collected for measurement of serum concentrations of AMG 340 as specified in the Schedule of Activities (Section 1.3). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

[redacted]

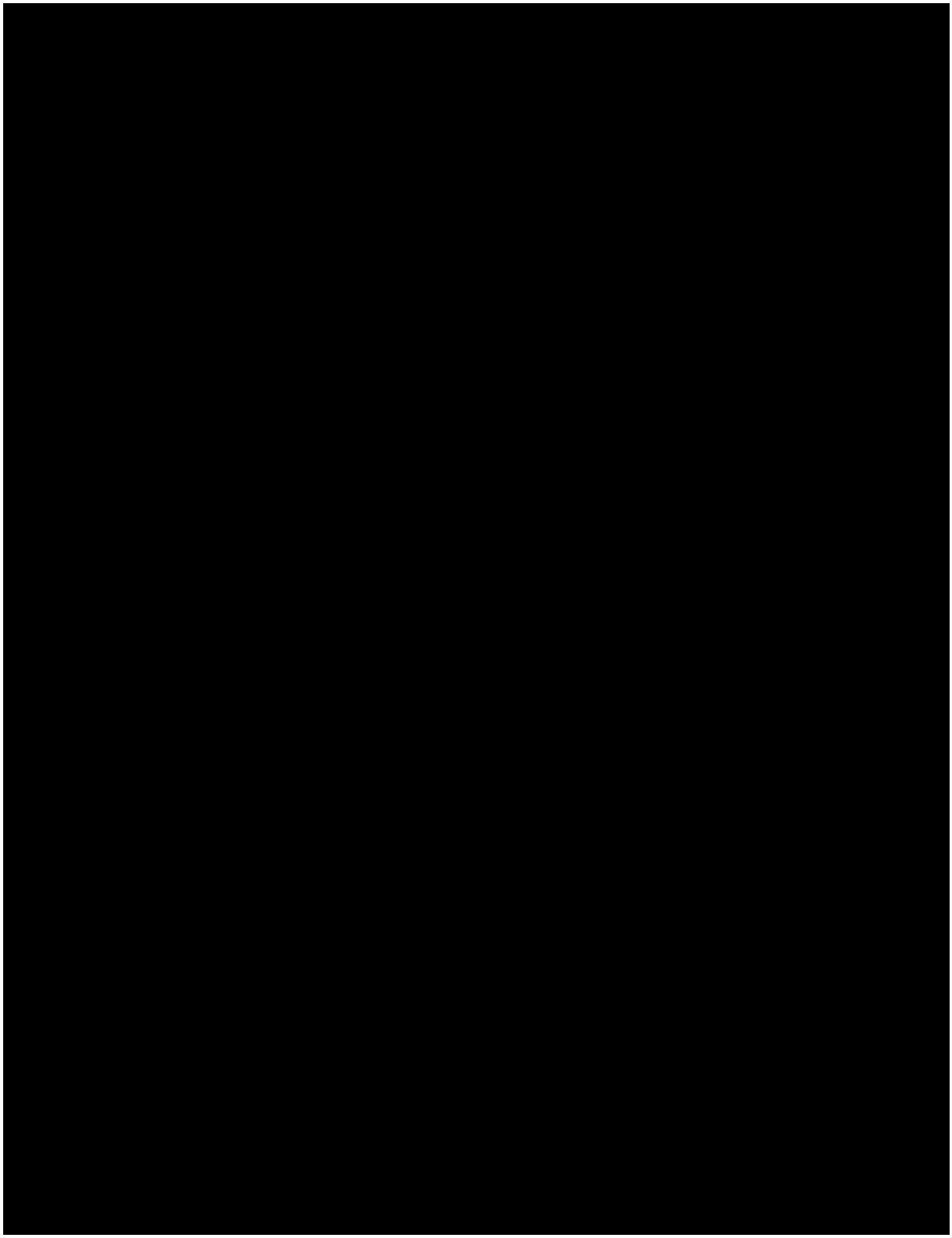
8.7 Antibody Testing Procedures

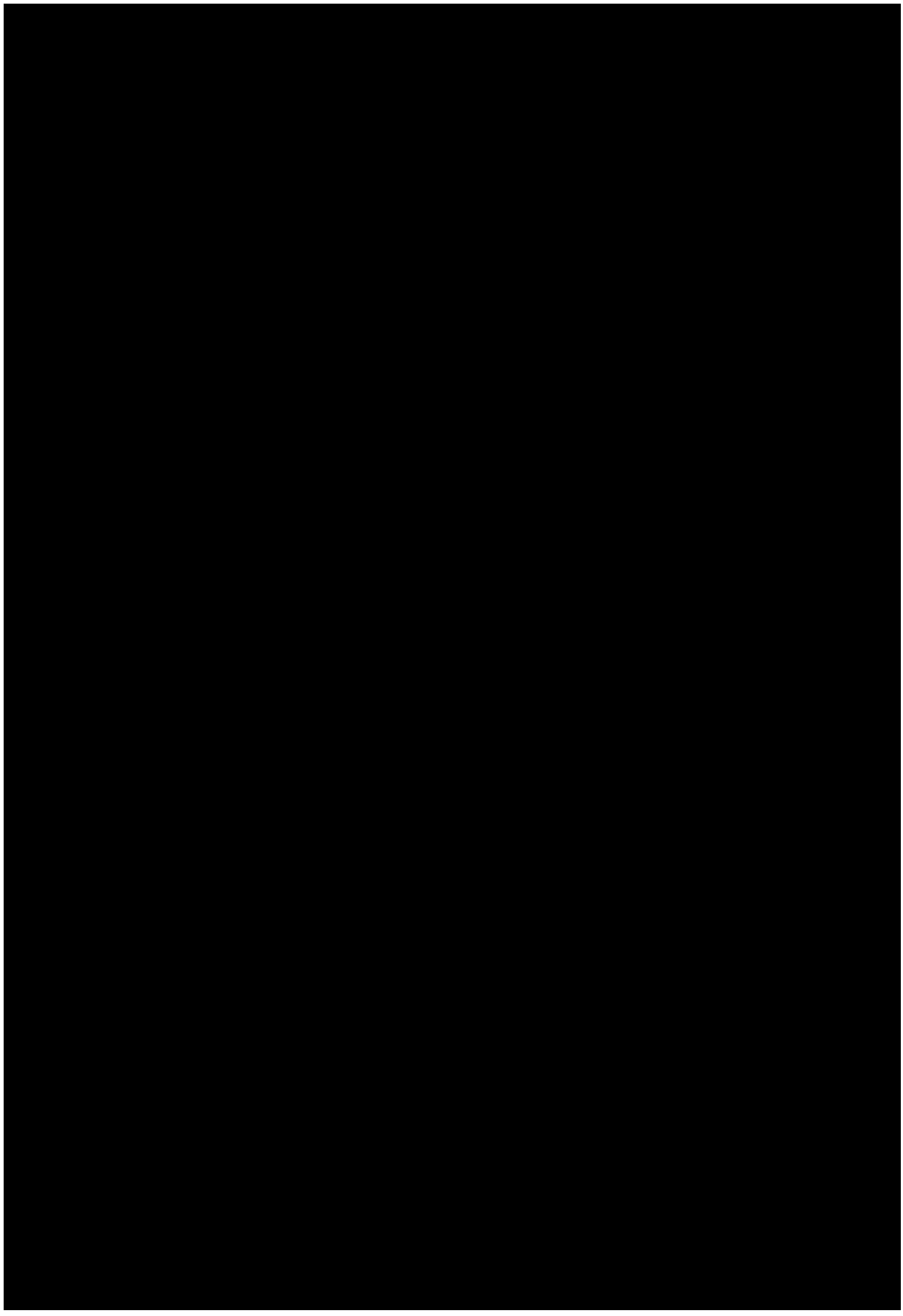
Blood sample(s) for antibody testing are to be collected according to the time points specified in the Schedule of Activities [redacted] for the measurement of anti-AMG 340 binding antibodies. Samples testing positive for binding antibodies may be further characterized. Additional blood samples may be obtained to evaluate any anti-AMG 340 antibody mediated impact on safety, PK and/or PD, and efficacy during the study. At the end of treatment time point or potentially earlier, whole blood will be collected to further characterize a possible antibody response.

Subjects who test positive for antibodies at the final scheduled antibody time point and have clinical sequelae that are considered potentially related to an anti-AMG 340 antibody response will also be asked to return for additional follow-up testing. This testing is to occur approximately every 3 months from the final scheduled antibody time point and continue until: (1) antibodies are no longer detectable; or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of AMG 340.

More frequent testing or testing for a longer period of time may be requested in the event of safety-related concerns.

Refer to the Schedule of Activities (Section 1.3), as applicable, for specific time points, and the laboratory manual for detailed collection and handling instructions.





9. Statistical Considerations

9.1 Statistical Hypotheses

In Part A, a safe and tolerable dose of AMG 340 will have evidence of anti-tumor activity in subjects with mCRPC as measured by ORR. In Part B, AMG 340 will improve ORR in subjects with mCRPC to 20% compared with the reference ORR of 5%.

9.2 Sample Size Determination

In Part A, at least 3 subjects are planned for enrollment into each cohort, with the goal of determining the MTD and/or RP2D of AMG 340. Approximately 60 subjects are anticipated in Part A; however, the total number of subjects in Part A will depend upon the occurrence of DLT events and how dose escalation progresses. If the unknown true toxicity rate/DLT rate is 33% in a given cohort, at least 2 DLTs are likely to be observed.

In Part B, up to 40 subjects will be enrolled to further evaluate safety and tolerability, to explore activity of AMG 340 and to evaluate the relationship between PD markers and PK, safety and clinical response. A sample size of 40 subjects was selected to achieve 92% power for testing the hypothesis on ORR at 1-sided alpha of 0.1 using the binomial exact test.

9.3 Populations for Analysis

The following populations are defined:

Population	Description
PK	subjects who have received at least 1 dose of AMG 340 and have at least 1 PK sample drawn post dose

ADA	subjects who have received at least 1 dose of AMG 340 and have at least 1 ADA sample drawn post dose
RECIST 1.1 Evaluable	subjects who have received at least 1 dose of AMG 340, have measurable disease per RECIST 1.1 at baseline and have the opportunity to be followed for at least 6 weeks from start of AMG 340 treatment.
PSA Response Evaluable	subjects who have received at least 1 dose of AMG 340, have a measurable (ie, > 0) PSA at baseline, and have the opportunity to be followed for at least 9 weeks from start of AMG 340 treatment.
DLT-evaluable	subjects who are evaluable for DLTs. A subject is considered "DLT Evaluable" if the subject has completed at least the first full treatment cycle or has experienced a DLT during the first treatment cycle
Safety	subjects who have received at least 1 dose of AMG 340

ADA = antidrug antibody; DLT = dose limiting toxicity; PK = pharmacokinetic; PSA = prostate specific antigen; RECIST = Response Evaluation Criteria in Solid Tumor

9.3.1 Covariates

Not applicable for this study.

9.3.2 Subgroups

[redacted]

9.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses.

9.4.1 Planned Analyses

9.4.1.1 Interim Analysis and Early Stopping Guidelines

Amgen will conduct evaluations of the treatment and outcome of the CRS events treated with siltuximab on an ongoing basis to assess if the threshold for pausing siltuximab treatment has been reached as outlined in the table below. If these stopping rules are met, an ad hoc DLRT will be triggered to review safety data and available PK, PD, and efficacy data. If recommended by DLRT, the use of siltuximab will resume. The stopping rules to trigger an ad hoc DLRT to review siltuximab treatment use a Bayesian approach proposed by Thall, et al (1995); an ad hoc DLRT will be triggered if the posterior probability that the CRS progression to grade 3 rate is greater than 30% is > 80% or the posterior probability that the CRS progression to grade 4 rate is greater than 10% is >80%; or observation of any grade 5 CRS after the event has been treated with

siltuximab. The stopping boundaries presented below assume a prior distribution of Beta (0.6, 1.4) for progression to grade 3 CRS and a prior distribution of Beta (0.2, 1.8) for progression to grade 4 CRS. The evaluations could occur more frequently if necessary to address emerging safety concerns. If the triggered ad hoc DLRT coincide with regular DLRT, they may be combined.

Table 9-1. The Criteria for Evaluating the Use of Siltuximab

	Trigger DLRM if severity of any CRS event treated with siltuximab progresses to Grade 5	
Number of subjects treated with siltuximab	Or the number of subjects with severity of CRS progressed to Grade 3 after being treated with siltuximab is	Or the number of subjects with severity of CRS progressed to Grade 4 after being treated with siltuximab is
5	≥ 3	≥ 2
10	≥ 5	≥ 3
15	≥ 7	≥ 3
20	≥ 8	≥ 4
25	≥ 10	≥ 5
30	≥ 12	≥ 5
35	≥ 13	≥ 6
40	≥ 15	≥ 6

CRS = cytokine release syndrome; DLRM = dose level review meeting

9.4.1.2 Primary Analysis

The primary analysis will occur 6 months following the enrollment of the last subject in Part B. The data will be analyzed once they have been entered, cleaned, and locked.

9.4.1.3 Final Analysis

The final analysis will occur after all subjects have ended the study. The data will be analyzed once they have been entered, cleaned, and locked.

9.4.2 Methods of Analyses

9.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety 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.

9.4.2.2 Efficacy Analyses

Endpoint/ Estimand	Statistical Analysis Methods
Primary	Not applicable
Secondary	The proportion of subjects with an OR per RECISIT 1.1 along with the corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934); similarly, the proportion of subjects, 95% CI will be tabulated for PSA response. Kaplan-Meier quartiles, rates and curves will be used to summarize OS, rPFS, 6-month landmark rPFS, PSA PFS, time to progression (radiographic and PSA), time to symptomatic skeletal events (SSE), and DOR.
[redacted]	

Listings may be provided instead of summary tables if the number of subjects for analysis is small.

9.4.2.3 Safety Analyses

9.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint/Estimand	Statistical Analysis Methods
Primary	Unless otherwise specified, statistical analyses on safety endpoints will be done using subjects from the Safety Analysis Set, which includes subjects that are enrolled and received AMG 340. The analysis of DLTs will be conducted on the DLT Analysis Set. Subject incidence of DLT will be tabulated by planned dose level. The statistical analysis methods for other safety endpoints are described in Sections 9.4.2.3.2 through 9.4.2.3.6. Descriptive statistics for the continuous variables and the frequencies/percentages for the discrete variables will be provided.

9.4.2.3.2 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to discontinuation from investigational product or other protocol-required therapies will also be provided.

A subgroup analysis of safety with CRS outcomes and PK will be performed for subjects who were administered siltuximab.

9.4.2.3.3 Laboratory Test Results

Clinical laboratory data will be reviewed for each subject. Depending on the size and scope of changes in laboratory data, the analyses of safety laboratory endpoints may include summary statistics over time and/or changes from baseline over time. Shifts in grades of safety laboratory values from baseline for selected laboratory values may also be provided.

9.4.2.3.4 Vital Signs

The analyses of vital signs will include summary statistics over time and/or changes from baseline over time.

9.4.2.3.5 Physical Measurements

The analyses of physical measurements will include summary statistics at baseline.

9.4.2.3.6 Electrocardiogram

The ECG measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.4.2.3.7 Antibody Formation

The incidence and percentage of subjects who develop anti-AMG 340 antibodies at any time will be tabulated overall and by planned dose level.

9.4.2.3.8 Exposure to Investigational Product

Descriptive statistics of cumulative dose, number of cycles, duration of usage, number and percentage of subjects with dose modifications and interruptions will be produced to describe the exposure to AMG 340.

9.4.2.3.9 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term or category as coded by the World Health Organization Drug dictionary.

9.4.2.4 Other Analyses

9.4.2.4.1 ECOG Performance Scores

The ECOG performance scores will be summarized by visit and change from baseline by visit.

9.4.2.4.2 Pharmacokinetic Analyses

Serum concentrations of AMG 340 and PK parameter values will be tabulated for each subject, each dose level, and summary statistics will be computed for each sampling time and each parameter.

Pharmacokinetic parameters of AMG 340 from a particular dosing schedule assessed on cycle 1 day 1 will be analyzed **according to the statistical analysis plan (SAP)**. An analysis will be performed for dose normalized C_{max} and dose-normalized AUC provided that they can be adequately determined from the data.

Additional analyses will be performed if useful and appropriate.

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11. Appendices

11.1 Appendix 1. List of Abbreviations

Abbreviation	Explanation
ADA	Antidrug antibody
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
ASR	Annual Safety Report
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_t	Area under the serum concentration-time curve from time zero to time of last measurable concentration
BOIN	Bayesian Optimal Interval
BRCA	Breast cancer gene
CaP	Prostate cancer
CAR	Chimeric antigen receptor
CARTOX	CAR-T-cell therapy associated toxicity
CBR	Clinical benefit rate
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed serum concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRS	Cytokine release syndrome
Css, trough	Trough concentration at steady state
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DLT	Dose limiting toxicity
DOR	Duration of objective response
DSUR	Development Safety Update Report
EC50	Half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
EOI	End of infusion
EOT	End of treatment
FDA	Food and Drug Administration
^{18}F-FDG	^{18}F-Fluorodeoxyglucose
FIH	First-in-human

Abbreviation	Explanation
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
[redacted]	
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure
ICE	Immune effector cell encephalopathy
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
IL	Interleukin
IMT	Immune mediated toxicity
IRB	Institutional Review Board
IRR	Infusion related reaction
IV	Intravenous
mAb	Monoclonal antibody
MABEL	Minimal anticipated biological effect level
mCRPC	Metastatic castrate-resistant prostate carcinoma
MED	Minimum efficacious dose
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor response
MRI	Magnetic Resonance Imaging
^{99m}Tc MDP	^{99m}technetium methylene diphosphonate
MTD	Maximum tolerated dose
NA	Not applicable
NCA	Noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NLCB	No longer clinically benefiting
NT	Neurotoxicity
ORR	Objective response rate
OS	Overall survival
PARPi	Poly-ADP-ribose-polymerase inhibitors
PBMC	Peripheral blood mononuclear cells
PC	Positive control
PCR	Polymerase Chain Reaction
PCWG3	Prostate Cancer Working Group 3
PD	Pharmacodynamic(s) or Progressive Disease

Abbreviation	Explanation
PET	Positron emission tomography
PI	Prescribing information
PK	Pharmacokinetic
PFS	Progression-free Survival
PO	Orally
PR	Partial response
PRO	Patient Report Outcomes
PSA	Prostate-specific antigen
PSA30	Rate of prostate-specific antigen decrease ≥ 30%
PSA50	Rate of prostate-specific antigen decrease ≥ 50%
PSMA	Prostate-specific membrane antigen
PT	Prothrombin time
Q3W	Once every 3 weeks
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
RLT	Radioligand therapies
rPFS	Radiographic progression-free survival
RP2D	Recommended phase 2 dose
RR	Relapsed or refractory
RT-PCR	Reverse transcriptase-polymerase chain reaction
SAP	**Statistical Analysis Plan**
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCT	Stem cell transplant
SD	Stable disease
SMG	Safety Monitoring Group
SSE	Time to symptomatic skeletal events
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$ or $T_{1/2}$	Terminal half-life
T-BsAbs	T-cell engaging bispecific antibodies
TLS	Tumor lysis syndrome
T_{max}	Time to maximum observed serum concentration
TNFα	Tumor necrosis factor alpha
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
US	United States
V_1	Central compartment volume
Vss	Volume of distribution at steady state
WHO	World Health Organization

11.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 11-1 will be performed by the local laboratory with the exception of the tests noted below. Additional analyte test results may be reported by the local or central laboratory, in accordance with standard laboratory procedures (eg, components of a hematology panel).

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 5.1 to 5.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 11-1. Analyte Listing

Local Laboratory: Chemistry	Local Laboratory: Coagulation	Local Laboratory: Urinalysis	Local Laboratory: Hematology	Other Lab Analytes
Sodium	PT/INR	Urobilinogen	RBC	Central Laboratory: [redacted]
Potassium	PTT/aPTT	Blood	Hemoglobin	
Chloride		Protein	Hematocrit	
Bicarbonate		Glucose	MCV	
Total protein		Bilirubin	MCH	
Albumin		Microscopic examination	MCHC	
Calcium			Platelets	
Magnesium			WBC	
Glucose			NLR	
BUN or Urea			Differential	Local Laboratory:
Creatinine			• Bands/stabs	Serum or Urine Pregnancy
Total bilirubin			Neutrophils (only %)	Testosterone
ALP			Eosinophils (if detected; absolute and %)	Hep B surface antigen
LDH			Basophils (if detected; absolute and %)	Hep C antibody
AST (SGOT)			Lymphocytes (absolute and %)	HIV Ab/Ag[a]
ALT (SGPT)			Monocytes (absolute and %)	
γ-glutamyl transferase				
B2-microglobulin				
CRP				
Ferratin				
d-dimer				
Fibrinogen				
Urine telopeptide				

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; HDL = high density lipoprotein; Hep = hepatitis; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; NLR = neutrophil to lymphocyte ratio; [redacted] PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; RDW = red cell distribution width; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

[a] HIV assessment is recommended.

[redacted]

If the subject is being followed for possible drug induced liver injury (DILI), the following analytes may be tested at the local laboratory depending on the clinical situation (see Appendix 7 [Section 11.7]).

Table 11-2. DILI Potential Analyte Listing

Chemistry	Total bilirubin, direct bilirubin, ALP, LDH, AST (SGOT), ALT (SGPT), creatine kinase, ferritin, gamma-glutamyl transferase, haptoglobin, CRP, fibrinogen, d-dimer
Hematology	Hemoglobin, Platelets, RBC Morphology, RBC Count, WBC Count, WBC Differential
Coagulation	PT, INR, APTT
Immunology	5 Prime Nucleotidase, Alpha-1 Antitrypsin, Antinuclear Antibodies, Anti-Smooth Muscle Antibody, Anti-Soluble Liver Ag/Liver-Pancreas Ag, Cytomegalovirus IgG Antibody, Cytomegalovirus IgM Antibody, Endomysial IgA Antibody, Epstein-Barr Virus EDA IgG Antibody, Epstein-Barr Virus NA IgG Antibody, Epstein-Barr Virus VCA IgG Antibody, Epstein-Barr Virus VCA IgM Antibody, Hepatitis A Virus IgG Antibody, Hepatitis A Virus IgM Antibody, Hepatitis B Core Antibodies, Hepatitis B Core IgM Antibody, Hepatitis B Surface Antigen, Hepatitis B Virus DNA Genotyping, Hepatitis B Virus Surface Antibody, Hepatitis C Antibodies, Hepatitis C Virus RNA Genotyping, Hepatitis D Virus Antibody, Hepatitis D RNA, Hepatitis E RNA, Hepatitis E IgG Antibody, Hepatitis E IgM Antibody, Herpes Simplex Virus Type 1_2 IgG AB, Herpes Simplex Virus Type 1_2 IgM AB, Human Herpes Virus 6 DNA, Human Herpes Virus 7 DNA, Human Herpes Virus 8 DNA, Immunoglobulin G, Liver Kidney AB 1, Parvovirus IgM/IgG Antibody, Serum Caeruloplasmin, Tissue Transglutaminase IgA Antibody, Toxoplasma IgM/IgG, Varicella Zoster Virus Antibody
Toxicology	Acetaminophen

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DILI = drug-induced liver injury; EDA = early antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; NA = nuclear antigen; PT = prothrombin time; RBC = red blood cell; RNA = ribonucleic acid; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; VCA = viral capsid antigen; WBC = white blood cell

11.3 Appendix 3. Study Governance Considerations

[redacted]

Dose Level Review Meetings (DLRM)

A DLRM is conducted to review and interpret safety data for the purposes of making recommendations about dose-level escalation (either to the next planned dose or to an intermediate dose), dose level de-escalation, subject group/cohort continuation, or cohort expansion; making recommendations about non-dose escalation subject group/cohorts (eg, expanded, highest dose and/or final subject group/cohort); and evaluating safety signals for purposes of applying Dose Group/Cohort Stopping Rules. The required DLRT members are the medical monitor, global safety officer (GSO), and

site investigators. The DLRT will include all site investigators. The medical monitor, GSO, and site investigators are the only voting DLRT members.

The medical monitor must be in attendance and cannot be represented by a voting designee or delegate. Voting designees can be identified as appropriate by the GSO or site investigator(s). A site investigator may identify a delegate (eg, sub-Investigator) who is listed in the Delegation of Authority. If a site investigator does this, the site investigator must provide written agreement with the designee or delegate's vote.

For a DLRM to occur, the medical monitor must attend, and the GSO or delegate must attend. In addition, a quorum of site investigators must be present (may occur at more than one meeting). A quorum is defined as greater than or equal to 50% of the participating investigators or their qualified designee. The DLRM will be rescheduled if these requirements are not met.

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, electrocardiogram (ECG), vital signs, and laboratory results will be reviewed.

Data will be reviewed blinded (ie, treatment assignment will not be revealed) unless unblinding is deemed necessary for the review team to make dosing recommendations. If deemed necessary, unblinding will be performed to assist dose change recommendations, in accordance with Amgen standard procedures.

Dose level review meetings voting will occur as follows: there will be a total of 3 votes, 1 for the medical monitor, 1 for the GSO or delegate, and 1 for all of the site investigators or delegates combined. Regardless of how many site investigators there are, all of the site investigators combined will have a total of 1 vote decided by a majority of the investigators (defined as greater than or equal to 50%).

DLRM recommendations to escalate to the next planned subject group/cohort, or to an intermediate subject group/cohort, must be by unanimous vote. If the voting members of the DLRT are not able to reach a unanimous recommendation on whether to escalate to the next planned subject group/cohort or to an intermediate subject group/cohort, then this should be reflected in the DLRM Memo. Other recommendations, such as expanding a subject group/cohort or lowering a dose will be made by a majority vote.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure (IB), and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. 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.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all protocol amendments and changes to the informed consent document that Amgen distributes to the site. 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.

During the course of the study, if new information becomes available that alters the benefit-risk of the study or the study drug, Amgen will follow applicable regulations to notify investigators, the IRB/IEC, and regulatory authorities, as appropriate.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Informed Consent Process

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 sample

informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 7.1.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally authorized representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 28 days from the previous informed consent form signature date.

The informed consent form (ICF) will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

The subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the case report form (CRF) demographics page, in addition to the unique subject identification number, include the age at 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 age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

Subject data should be kept in a secure location. Access to subject data will be limited to authorized individuals, as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Amgen complies with all relevant and applicable laws and regulations that protect personal information in order to ensure subject confidentiality and privacy. Subjects are designated by a unique subject identification number in the sponsor's systems. The sponsor uses access-controlled systems to house, review and analyze subject data. These systems are backed-up regularly to minimize the risk of loss of subject data; procedures are also defined for data recovery in the event of data loss. The sponsor has standard operating procedures in place that restrict access to subject data to those who require access to this data based on their role and have also completed the required training. These procedures also outline the process for revoking access to such data when it is no longer needed. In the event of a security breach, the sponsor has procedures in place for notification of privacy incidents and to address these incidents, via its Business Conduct Hotline.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does

not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work 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 need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must 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 must qualify for authorship, and all those who qualify are to be listed. Each author must 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 review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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 CRFs, are resolved.

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, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit 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.

Quality tolerance limit parameters (QTLs) will be predefined in the QTL definitions table to identify possible systematic issues that can impact participant safety and/or reliability

of the study results. These predefined parameters will be monitored during the study. Important deviations from the QTL threshold limits for these parameters and remedial actions taken will be summarized in the clinical study report.

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

Case Report Forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

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 CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF 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. Source documents may also include data captured in the IRT system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment or certain demographic information, such as gender, race, and ethnicity).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 CRFs, 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, 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

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

Remote Source Data Review and Verification

If permitted by national and/or local regulations, remote Source Data Review and Verification (rSDR/V) can be implemented. The clinical monitor should be provided with a secure, read-only access to the Electronic Medical Record (EMR) system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object to remote access to their medical records. A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorized access, access rights should be revoked once rSDR/V tasks have been completed for the trial. The EMR system should have an audit trail and be able to log information on who accessed data and when. Remote access to the EMR should only be possible using a two-factor authentication.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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(s) by a separate 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 the product(s) is/are available commercially.

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.

11.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the Statistical Analysis Plan (SAP).
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • For situations when an adverse event or serious adverse event is due to mCRPC 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 adverse event. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event

Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event/serious adverse event information in the Events case report form (CRF).
- The investigator must assign the following mandatory adverse event attributes:
  - Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  - Dates of onset and resolution (if resolved);
  - Did the event start prior to first dose of investigational product
  - Assessment of seriousness;
  - Severity (or toxicity defined below);
  - Assessment of relatedness to investigational product(s), other protocol-required therapies, and/or study-mandated activity and/or procedures, including [redacted] and ^{18}F-FDG
  - Action taken; and
  - Outcome of event.
- If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Event CRF.
- It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor/responsible contact research organization (CRO) in lieu of completion of the Events CRF page.
- 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. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity

The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

The Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 which is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

The adverse event grading scale to be used for this study will be the CTCAE and is described in Section 11.4. CRS, which will be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 11.10) and TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 11.11), and ICANS will be using the criteria referenced in the publication by Lee et al (2019) (see Section 6.2.1.6.1.1).

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s) protocol-required therapies, and/or study-mandated activity and/or procedure(s), including [redacted] ^{18}F-FDG, and each occurrence of each adverse event/serious
- Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality.

- There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.
- The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed Events CRF.
- The investigator will submit any updated serious adverse event data to Amgen immediately and no later than 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Paper CRF

- Facsimile transmission of the Serious Adverse Event Report Form (see Figure 11-1) is the preferred method to transmit this information.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the Serious Adverse Event Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Serious Adverse Event Report Form within the designated reporting time frames.
- Once the study has ended, serious adverse event(s) suspected to be related to investigational product will be reported to Amgen if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Report Form to report the event.

Figure 11-1. Sample Serious Adverse Event Report Form (paper-based form)

The following minimum fields must be completed prior to faxing the form:
1) Site Number; 2) Subject ID Number; 3) Serious Adverse Event Diagnosis; Serious Criteria Code; Start Date of Event; 10) Signature
Ensure both pages are faxed with each submission.

Note: Only events that meet serious criteria (regardless of causal relationship to IP) should be reported on this form. Submit a Serious Adverse Event Report (SAER) form within 24 hours of the Investigator's knowledge of the event. *Indicates a mandatory field.

Data on the AE Summary CRF (also known as Events CRF) must agree with data submitted on the SAER form in the following areas: adverse event term(s), serious criteria, and relationship of product to event.

Only include information that is relevant (pertinent) to the event(s) included on this SAER (eg, concomitant medications, medical history, laboratory and diagnostic tests)

Header Information

New / Follow-up – Indicate if this is a new adverse event, or a follow-up of a pre-reported event.

Follow-up – Send a follow-up report if additional data adds to or changes the clinical interpretation of the event. Some examples are:

- The initial reported event has changed and additional serious criteria have been met (such as if event outcome is now fatal).
- Signs and symptoms were reported at the time of the initial report and a final diagnosis has now been made.
- A change in relationship of a study procedure or activity has occurred from the initial report.
- A significant change has occurred in the start date of the event or start date of a suspect concomitant medication.
- Additional concomitant medications and/or diagnostics have been identified that may contribute to or explain the event.

When sending a follow-up report, either:

- On a photocopy of the prior report, add the additional information, re-sign and date, then fax in the follow-up form – or –
- Complete a new form with the new information. If the serious adverse event terms have not changed, please write, in section 3, the following: "No changes in serious adverse event terms from previous SAER form," then fax in the follow-up form.
- If a new serious adverse event term is to be added to the terms previously reported, add this new term to a photocopy of the initial form.
- If an earlier reported adverse event is being replaced by a new diagnosis or event term, on a photocopy of the initial report, strike through the term to be deleted, sign and date the deletion and add the updated event term.

1. Site Information

Site Number* – Enter your assigned site number for this study

Investigator*, Country*, Date of Report, Reporter*, Phone No., and Fax No. – Enter information requested

2. Subject Information

Subject ID Number* – Enter the entire number assigned to the subject **Age at event onset, Sex, and Race** – Enter the subject's demographic information

End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

3. Serious Adverse Event

Provide the date the Investigator became aware of this Serious Adverse Event Information

Serious Adverse Event Diagnosis or Syndrome* –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available. Do not enter "Death," as this is an outcome, not an event.

Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalizion. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field**.

Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal/resulted in death, enter the date of death as the end date

If event occurred before the first dose of investigational product, add a check mark in the corresponding box.

Serious Criteria Code* - This is a mandatory field for serious events – Enter reason why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria,"**Other medically important serious event**"' may be the appropriate serious criterion.

Relationship to IP* – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (eg, prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (eg, heating pads, infusion pumps)**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**

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Instruction Page **1** of **2**

- Resolved – End date is known
- Not resolved/Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication administration – only diagnostic tests or activities mandated by the protocol.

4. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study, which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt. However, if the subject is retained in the study unit and becomes an inpatient due to an adverse event, the event would be reportable as a serious adverse event.

5. Investigational Product including Lot # and Serial # when known / available

Investigational Product – If applicable, indicate whether the Investigational Product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

6. Concomitant Medications

Indicate if there are any concomitant medications, including protocol-specified diluents and challenge agents.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is suspect for the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

10. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). **If necessary, provide additional pages to Amgen.**

Footer

Signature, Title and Date* – The Investigator or designee must sign the form and provide his or her title and date and fax form to Amgen. If the reporter is not the Investigator, Designee must be identified on the Delegation of Authority form.

A 20210249 (TNB585.001) *AMG 340/TNB-585*	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

<<Fax number to be populated by COM/Study Manager/Protocol Author prior to providing to sites>> *SELECT OR TYPE IN A FAX#*

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report Day Month Year

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

3. SERIOUS ADVERSE EVENT - ***Information in this section must also be entered on the Serious Adverse Event Summary CRF***

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *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 co-curred before first dose of IP	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? If yes see section 10 AMG 340/ TNB-585 No Yes 68Ga-PSMA-11 No Yes 18F-FDG No Yes <Device> No Yes <Device> No Yes	Outcome of Event 01 Resolved 02 Not resolved 03 Fatal 04 Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life- threatening; **03** Required hospitalization; **04** Prolonged hospitalization; **05** Persistent or significant disability /incapacity; **06** Congenital anomaly / birth defect; **07** Other medically important serious event

4. HOSPITALIZATION

	Date Admitted Day Month Year	Date Discharged Day Month Year
Was subject hospitalized or was a hospitalization prolonged due to this event? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date 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 340/TNB-585 √Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown
68Ga-PSMA-11 √Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown
18F-FDG √Open Label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unknown
<<IP/Device>> ☐Blinded ☐Open Label							Lot # _____ ☐ Unknown Serial _____ ☐ Unknown

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A 20210249 (TNB585.001) *AMG 340/TNB-585*	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Concomitant 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

A 20210249 (TNB585.001) *AMG 340/TNB-585*	**Clinical Trial Serious Adverse Event Report – Phase 1–4** *Notify Amgen Within 24 Hours of knowledge of the event*	❑New ❑Follow-up

	Site Number	Subject ID Number	

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

Signature of Investigator or Designee	Title	Date
_____ *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.*		

11.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for males are outlined in Section 5.2. Contraceptive use and methods should be consistent with local regulations for subjects participating in clinical studies.

Male subjects should be advised of the pregnancy prevention requirements and the potential risk to the fetus if they father a child during treatment and for 6 months after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include documented hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Females with documented permanent infertility due to an alternate medical cause (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), can be considered not of childbearing potential.

Note: Bilateral tubal ligation/occlusion is not considered a permanent sterilization method.

Note: Documentation from the following sources is acceptable to provide confirmation of each sterilization method: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

A postmenopausal female is defined as:

- A woman of ≥ 55 years with no menses for 12 months without an alternative medical cause OR
- A woman age < 55 years with no menses for at least 12 months and with a follicle-stimulating hormone (FSH) level within the definition of "postmenopausal range" for the laboratory involved. In the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.

Contraception Methods for Females

Highly Effective Contraceptive Methods

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormonal-releasing system
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 6 months after the last dose of protocol-required therapies

The female partner should consider using a method of contraception for female subjects stated above (a female condom should not be used because there is a risk of tearing when both partners use a condom).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Collection of Pregnancy Information

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 6 months after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Form. The form (see Figure 11-2) must be submitted to Amgen Global Patient Safety immediately and no later than 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

- Males with pregnant partners or whose partners become pregnant during treatment and for an additional 6 months after the last dose of protocol-required therapies must practice sexual abstinence or use a condom through 6 months after the last dose of protocol-required therapies.
- The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Figure 11-2. Pregnancy Notification Form

Amgen Proprietary - Confidential

AMGEN® Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20210249 (TNB585.001)

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 age (at onset):**____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
AMG 340 / TNB-585				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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

11.6 Appendix 6. Sample Storage and Destruction

Any blood (eg, biomarker, pharmacokinetics) sample collected according to the Schedule of Activities (Section 1.3) 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 metastatic castrate-resistant prostate carcinoma, the dose response and/or prediction of response to AMG 340, 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 sample types (eg, blood, tumor) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

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.

11.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary 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 or hepatotoxins, 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-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 11-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 11-3) are never to be rechallenged.

Drug-induced Liver Injury Reporting and 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 the above, require the following:

- The event is to be reported to Amgen as a serious adverse event immediately and no later than 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate case report form (CRF) (eg, Events CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to 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 11.4.

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 Table 11-3 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated 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 (BIL) (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 with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 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
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase 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 a 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 the corresponding CRFs.

11.8 Appendix 8. Eastern Cooperative Oncology Group (ECOG) Performance Score

Grade	ECOG
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.

11.9 Appendix 9. Activity Measurements

Table 11-4. Response Categories Based on Assessment of Target Lesions

	Complete Response	Partial Response	Stable Disease	Progression of Disease
Measurable lesions	• Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.	• ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.	• ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). • The sum of diameters of target lesions must also demonstrate an absolute increase of at least 5 mm. • The appearance of 1 or more new lesions.
Non-measurable lesions	• Disappearance of all lesions.	Not applicable	Not applicable	• Unequivocal progression of non-measurable lesions. • The appearance of 1 or more new lesions.
Bone lesions	• Disappearance of all lesions.	Not applicable	Not applicable	• At least 2 new lesions on first post-treatment scan, with at least 2 additional lesions on the next scan (2+2 rule). o If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented. o For scans after the first post-treatment scan, at least 2 new lesions relative to the first post-treatment scan confirmed on a subsequent scan.
PSA	Not applicable	Not applicable	Not applicable	An isolated PSA increase is not sufficient for PD per PCWG3

PCWG3 = Prostate Cancer Working Group 3; PD = progressive disease; PR = partial response; PSA = prostate-specific antigen.
Source: Eisenhower et al, 2009; Scher et al, 2016.

Table 11-5. Time Point Response: Subjects with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluated; PD = progressive disease; PR = partial response; SD = stable disease.
Source: Eisenhower et al, 2009.

Table 11-6. Time Point Response: Subjects with Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/ Non-PD[a]
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = note evaluated; PD = progressive disease; SD = stable disease.
[a] Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.
Source: Eisenhower et al, 2009.

11.10 Appendix 10. Specific Guidance for Cytokine Release Syndrome

Cytokine release syndrome (CRS) 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 initial injection or infusion of AMG 340. CRS may be life threatening or fatal. Injection or infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the treatment with AMG 340, 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 Section 11.10 (based on the adopted grading system referenced in Lee et al, 2019).

Please also refer to the general guidance for re-start of injection or infusion after interruptions/delay/withholding and dose modifications in Section 6.2.2.4.

For grade 3 and 4 CRS, please also see Section 6.2.1.4.1 for dose-limiting toxicity (DLT) considerations. Fever reported outside the context of CRS will be graded per CTCAE version 5.

11.11 Appendix 11. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 classifies tumor lysis syndrome (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 5.0. 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 and clinical TLS (see Table 11-8) including grading.

Based on the Cairo and Bishop system, laboratory TLS is defined as any 2 or more abnormal serum values present within 3 days before or 7 days after initiation of treatment in the setting of adequate hydration (with or without alkalinization) and use of a hypouricemic agent (Table 11-7).

Table 11-7. 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 tumor lysis syndrome.

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. The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 11-8.

Table 11-8. 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

Grade	Creatinine[a, b]	Cardiac arrhythmia[a]	Seizure[a]
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.

11.12 Appendix 12. RECIST 1.1 With Prostate Cancer Working Group 3 (PCWG3) Modifications

Imaging provides critical information on disease distribution, prognosis, extent, biology, and host reaction to the tumor. Detailed imaging instructions are provided in the imaging manual. The following Prostate Cancer Working Group 3 (PCWG3) recommendations are provided as a reference (Scher et al, 2016):

Baseline by Site of Disease

PCWG3 retains the PCWG2 recommendations with modifications that include developing, recording, and validating measures of disease burden. Imaging of the chest, abdomen, and pelvis using a contrast-enhanced computed tomography (CT) scan with ≤ 5-mm axial slices is advised for all patients. For those intolerant of iodinated contrast, a cross-sectional magnetic imaging resonance (MRI) scan with contrast of the abdomen and pelvis, with a non-contrast CT scan of the chest, may be considered. In phase 1 and **2** trials, recognizing that individual lesions may be biologically distinct, PCWG3 recommends reporting whether progression on entry was in the growth of pre-existing lesions, the development of new lesions, or both. PCWG3 advises following Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for extraskeletal disease but recommends that up to 5 lesions per site of metastatic spread (eg, lung, liver, lymph nodes as separate sites) be recorded to address disease heterogeneity and to track patterns of metastatic progression. Bone lesions should be recorded separately.

Prostate or prostate bed

Specific imaging of the prostate or prostate bed is not required for every patient. If there is a question of locally persistent or recurrent disease, a directed MRI of the prostate or prostate bed and/or biopsy of the site is recommended.

Nodes or viscera

PCWG3 advises that nodal disease be measured in the short axis and recorded by location: pelvic disease should be classified as locoregional, and extrapelvic disease (retroperitoneal, mediastinal, thoracic, or other) as metastatic. Nodes ≥ 1.5 cm in the short axis are considered pathologic and measurable. As per RECIST 1.1, lymph nodes that are ≥ 1.0 cm but less than 1.5 cm in the short axis may be pathologic and can be considered non-measurable/nontarget lesions. Visceral disease in metastatic patients should be designated separately as lung, liver, adrenal, or central nervous system (CNS) and is considered measurable if an individual lesion is ≥ 1 cm in its longest dimension.

Given that lung metastases are relatively frequent in metastatic castration-resistant prostate cancer (mCRPC) trials (7% prevalence), chest CT imaging is recommended.

Bone

The use of ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) radionuclide bone scintigraphy as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form and the "2+2" rule set. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Neurologic

PCWG3 upholds the PCWG2 recommendation to perform an MRI or CT of the brain for patients with small-cell/neuroendocrine tumors and to maintain a low threshold for performing an MRI of the base of the skull or spine to diagnose and/or detect impending neurologic compromise. Routine imaging of the brain for adenocarcinoma is not recommended.

Type of progression at entry into a trial

PCWG3 advises recording whether progression was manifested by prostate-specific antigen (PSA) alone, bone ± nodes by location, nodes by location only, or viscera (± other sites), and the proportion of patients who progress in each of these categories, because this is prognostic. PCWG3 also advises reporting whether progression by imaging at study entry involved the growth or enlargement of pre-existing lesions, the development of new lesions, or both.

NLCB: Progression Versus the Decision To Discontinue Therapy

PCWG2 encouraged the continuation of treatment if a rising PSA or worsening of an isolated disease site that was not clinically significant was the sole indicator of disease progression and the patient was otherwise tolerating therapy. Now, recognizing the biologic heterogeneity of individual metastatic lesions, PCWG3 draws the distinction between documenting progression for consistency of reporting (eg, recording the date of

documented progression in a site of disease such as a lymph node that is unlikely to adversely affect prognosis) versus the decision to stop therapy.

To address this, PCWG3 introduces the no longer clinically benefiting (NLCB) reporting metric defined as the date and the specific reason(s) a therapy was ultimately discontinued. This endpoint permits individualized provider-patient decisions to continue or discontinue a treatment based on the primary therapeutic objective for which it is being administered and assessed, be it quality of life, Patient Reported Outcomes (PROs), or survival. As an example, in cases in which multiple sites of disease continue to respond but 1 to 2 sites grow, focal therapy such as radiation or surgery could be administered to the resistant site(s) and systemic therapy continued. Similarly, therapy may be continued if progression by PSA or imaging is slow and the disease-related symptoms that were present at baseline remain controlled. Important here is to record in detail the specific reasons why a therapy was ultimately discontinued, which may include clinical deterioration (clarifying whether it is disease or therapy related) or need for a change in systemic therapy. PCWG3 cannot define the risks/benefits at the individual level for continuation of therapy beyond progression, but sets the goal of prospectively defining the circumstances in which scenarios are identified where continuing a therapy is justified. Clinical trials evaluating whether therapy A should be stopped and a new one started, continued alone, or continued with a new one added, are ongoing.

Source: Scher et al, 2016.

Amendment 5

Protocol Title: A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)

Amgen Protocol Number: 20210249 (formerly TNB585.001)

EudraCT number: Not applicable

NCT number: NCT04740034

Amendment Date: 07 December 2022

Rationale:

This protocol is primarily being amended to include a second priming dose at cycle 1 day 5 as >10-fold increases in the individual steps may not effectively mitigate the incidence and severity of the adverse drug reaction of cytokine release syndrome (CRS), an adverse event associated with T cell engager therapy. The new step dosing schedule in cycle 1 will be [redacted] mg on day 1, [redacted] mg on day 5, with the target dose of [redacted] mg to be administered on day 8. The addition of step doses has been successful in mitigating CRS while increasing early exposure and efficacy. [redacted]. Additional language was included to update and/or clarify other items in the protocol. Changes including, but not limited to, the following were incorporated into the protocol:

- Updated text and [redacted] Schedule of [redacted]
- Text and Table 6-6. AMG 340 Dose Modification Guidelines for Adverse events were updated to reflect current template language regarding management of both COVID-19 and Monkeypox Infection.
- Exclusion criterion 214 was removed and replaced with a more general statement regarding active systemic infection as COVID moves into an endemic phase.

- Statistical analyses language in 9.4.2.4.2 was removed in the protocol for presentation in the Statistical Analysis Plan.
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 4

Protocol Title: A Multicenter, Phase 1, Open-label, Dose escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)

Amgen Protocol Number AMG 340 20210249

NCT Number NCT04740034

Amendment Date: 26 September 2022

Rationale:

This protocol has been amended to incorporate the following key revisions.

- Updated key safety risks to add thrombocytopenia as a sign of cytokine release syndrome (CRS) based on safety evaluation of the study drug (Table 2-2 and Table 6-6).
- Reduced total number of subjects enrolled in the study. Number of subjects anticipated to be enrolled in part A (dose escalation) was decreased from 100 to 60 subjects to align with the Clinical Development Plan and in part B (dose expansion) was increased from 30 to up to 40 subjects to address regulatory mandate of dose optimization (Sections 1.1, 1.2, 4.1, and 9.2).
- Updated monotherapy [redacted], and activity data (Section 4.1.1).

The following updates are considered minor adjustments supporting the continuous effort to align this protocol to other Amgen internal protocols within the prostate portfolio as well as ensuring alignment with AMG 160 and AMG 509.

- Removed electrocardiogram (ECG) from the primary endpoints since statistical analyses of ECG measurements are not planned and the schedule of activities only include ECG assessment during screening (Sections 1.1 and 3).
- Added 6-month landmark radiographic progression-free survival as a secondary endpoint to evaluate clinical activity of study drug (Sections 1.1, 3, 9.4.2.2).
- Clarified definition of 'line/regimen of therapy' as it is a key factor defining the study population (Sections 1.1, 4.1).
- Provided important clarifications for timing of the safety follow-up (SFU) visit and recording of concomitant medication/therapy (Sections 1.3, 6.7.2, 7.1, 8.1.3, Table 1-1).
- Updated survival follow-up/long-term follow-up to specify the surveillance methods and period which extends for up to a maximum of 3 years from the last SFU visit occurring every 6 months (Table 1-1 and Section 8.1.4).
- [redacted]) regarding the on-treatment biopsy to guide physicians to discuss the biopsy collection process with subjects and conduct it only if feasible and safe. An additional update was to clarify definition of 'end of infusion' to ensure consistency across all study sites.
- Added a [redacted] only for end of treatment visit. Removed a timepoint for [redacted] for the safety follow-up visit [redacted]
- Updated procedures and schedule for radiologic assessments (Table 1.3 and Section 8.3).
- Updated inclusion criteria (Section 5.1) to:
    - Add that subjects must demonstrate adequate platelets and hemoglobin levels without platelet and blood transfusion, respectively, within 7 days from screening assessment (code 108)

- Increase the minimum value for the estimated glomerular filtration rate (eGFR) to ≥ 50 mL/min (code 109)

- Updated exclusion criteria (Section 5.2) to:
  - Provide a 2-year window from enrollment for diagnosed or treated malignancies with potential to interfere with the safety or efficacy assessments of the investigational regimen. Additionally, examples for exceptions to this exclusion criterion were listed (code 201)
  - Add pathological findings that must be excluded, such as histology of pure small cell, neuroendocrine carcinoma of the prostate and any other histology different from adenocarcinoma (code 202)
  - Increase window prior to first dose of study treatment for subjects who have undergone major surgical procedures to 28 days. Provide specific windows from first dose of study treatment for subjects that have received radiotherapy and include language to define palliative care regarding radiation therapy (code 208 and Section 6.1.7).
  - Clarify that not all active infections are considered as an exclusion criterion and provide specific examples of infections that are permitted if responding to treatment (code 209).
  - Update window for major cardiac abnormalities from 12 weeks to within 12 months of first dose of study treatment and decrease corrected QT prolongation to > 470 msec (code 210).
  - Update to align general infection language to the new Bispecific T-cell Engager (BiTE®) Covid guide for Phase 1 Protocols of BiTE® Molecules in Early Development (code 214).

- Updated and clarified information regarding excluded treatments, medical devices, and/or procedures during study period (Section 6.1.7).

- Clarified dose limiting toxicity (DLT) definition for dose escalation to specify that up to 3 priming doses of study drug will be equivalent to 1 dose of study drug within the duration of the DLT observation period (Section 6.2.1.4.1).
- Added a guide for re-start of intravenous (IV) infusion administration in case of infusion interruptions or delays due to technical or logistical issues (Section 6.2.2.2).
- Included additional guidance regarding management of overdose and for reporting of adverse events possibly related to overdose (Section 6.6).
- Included guidance for the use of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, live vaccines, and live-attenuated vaccines during screening and treatment period (Section 6.7.2.1).
- Added that as part of the medical history, known prostate cancer (CaP) mutations (eg, breast cancer gene 1 [BRCA1] and breast cancer gene 2 [BRCA2]) should also be recorded (Section 8.2.3).
- Included guidance for conduction of neurological examination as part of the physical examination (Section 8.2.4.1).
- Included information regarding the process for radiographic assessments to evaluate efficacy of AMG 340 treatment (Section 8.3).
- Clarified language describing analyses of primary safety endpoints (Section 9.4.2.3.1).
- Added an Appendix for RECIST (Response Evaluation Criteria in Solid Tumor) 1.1 with Prostate Cancer Working Group 3 (PCWG3) modifications (Appendix 12).
- Updated collection and reporting of safety events to align with current procedures described in the protocol template (Table 1-1, Table 1-3, Sections 8.4.6.1.1, 8.4.6.1.2, 8.4.6.1.3, 8.4.6.3, 8.4.6.4, 8.4.6.6, Appendix 11.4, Appendix 11.5).
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 3

Protocol Title: A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)

Amgen Protocol Number AMG 340 (formerly TNB-585) 20210249 (formerly TNB585.001)

NCT Number: NCT04740034

Amendment Date: 04 May 2022

Rationale:

This protocol is being amended to:

- Based on the biological mechanism, non-clinical data and clinical experience, cytokine release syndrome (CRS) was designated as an adverse drug reaction. The protocol is being updated with CRS as a key safety risk in Section 2.3.1.
- Update with available clinical data for AMG 340 as per Investigator's Brochure.
- Added timepoint to better define the [redacted] and duration of change.
- Other minor administrative/editorial corrections to improve readability and clarity of the protocol.

Amendment 2

Protocol Title: A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of AMG 340, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-resistant Prostate Carcinoma (mCRPC)

Amgen Protocol Number AMG 340 (formerly TNB-585) 20210249 (formerly TNB585.001)

NCT Number: NCT04740034

Amendment Date: 18 March 2022

Rationale:

The main driving force of this amendment was to bring this study into the current Amgen protocol template. The original version (dated 11 December 2020) and Amendment 1 (dated 21 December 2021) were authored using the TeneoBio protocol template. All text from these versions have been transcribed into the current Amgen protocol template. Only study-specific changes from Amendment 1 to Amendment 2 are described specifically in this document and associated tracked changes.

Other key changes are highlighted below:

- The [redacted] and schedule have been amended to align this study with the current Amgen [redacted]

Amendment 1

Protocol Title: A Multicenter, Phase 1, Open-label, Dose-escalation and Expansion Study of TNB-585, a Bispecific Antibody Targeting PSMA in Subjects with Metastatic Castrate-Resistant Prostate Carcinoma

Amgen Protocol Number AMG 340 Study 20210249

Amendment Date: 21 December 2021

Rationale:

This protocol is being amended to optimize safety on the study in accordance with Amgen standards and practice. The following changes are included in this amendment:

- Update new contact and reporting information.
- Update safety language to align with Amgen standard procedures and practice.
- Update CRS mitigation and management measures to reduce CRS incidence and severity.
- Update dose escalation plan to investigate priming doses and smaller dose increments between dose levels.
- Increase sample size in Arm A from 42 subjects to 100 subjects to accommodate investigations of intermediate dose levels, and of different priming and target dose combinations.
- Add language to allow siltuximab use when tocilizumab is not available per FDA guidance provided to Amgen.