Title Page

Protocol Title:		A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer
Short Protocol Title:		A Phase 1 Study of AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer
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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 (ICH E6).

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I have read the attached protocol entitled A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer, dated 16 March 2022, and agree to abide by all provisions set forth therein.

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_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Table of Contents

Table of Contents 4

1. Protocol Synopsis 12

2. Study Schema and Schedule of Activities 25
   - 2.1 Study Schema 25
   - 2.2 Schedule of Activities 29

3. Introduction 55
   - 3.1 Study Rationale 55
   - 3.2 Background 57
     - 3.2.1 Disease 57
     - 3.2.2 Amgen Investigational Product Background 59
       - 3.2.2.1 AMG 160 59
       - 3.2.2.2 Part 3 only: Etanercept 65
     - 3.2.3 Non-Amgen Investigational Product Background 66
       - 3.2.3.1 Pembrolizumab (Part 2 Only) 66
   - 3.3 Benefit/Risk Assessment 66
     - 3.3.1 Therapeutic Context 67
     - 3.3.2 Key Benefits 68
     - 3.3.3 Key Risks 69
       - 3.3.3.1 AMG 160 69
       - 3.3.3.2 Pembrolizumab (Part 2 only) 70
       - 3.3.3.3 Etanercept (Part 3 only) 72

4. Objectives, Endpoints and Hypotheses 74
   - 4.1 Objectives and Endpoints 74
   - 4.2 Hypothesis 77

5. Study Design 77
   - 5.1 Overall Design 77
     - 5.1.1 Part 1: AMG 160 Monotherapy 77
     - 5.1.2 Part 2: AMG 160 Combination with Pembrolizumab 78
     - 5.1.3 Part 3: Etanercept Prophylaxis for AMG 160-related CRS 79
     - [redacted]
     - 5.1.6 Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort 81
   - 5.2 Number of Subjects 82
     - 5.2.1 Replacement of Subjects 82
     - 5.2.2 Number of Sites 83

5.3 End of Study 83
5.3.1 End of Study Definition 83
5.3.2 Study Duration for Subjects 83
5.4 Justification for Investigational Product Dose 84
5.5 Patient Input on Study Design 86

6. Study Population 86
6.1 Inclusion Criteria 87
6.2 Exclusion Criteria 88
6.3 Subject Enrollment 91
6.4 Screen Failures 91

7. Treatments 92
7.1 Treatment Procedures 93
7.1.1 Investigational Products 93
7.1.1.1 AMG 160 and Pembrolizumab 93
[redacted]
7.1.1.4 Part 3 Only: Amgen Investigational Product: Etanercept 100
7.1.1.5 Non-Amgen Investigational Imaging Products 101
7.1.2 Non-investigational Products 101
[redacted]
7.1.4 Other Protocol-required Therapies 101
7.1.4.1 Premedication 102
7.1.4.2 Part 6 Only: Modified Cooperstown 5+1 CYP Phenotyping Cocktail 102
7.1.5 Other Treatment Procedures 103
7.1.6 Product Complaints 103
7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period 103
7.2 Method of Treatment Assignment 104
7.3 Blinding 104
7.4 AMG 160 Dose Determination and Dose Modification 104
7.4.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules 104
7.4.1.1 Dose-exploration Phase 104
7.4.1.2 Dose-expansion Phase 110
7.4.1.3 Dose-limiting Toxicity 111
7.4.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation 112
7.4.2.1 Amgen Investigational Product: AMG 160 112

7.4.2.2 Non-Amgen Investigational Product: Pembrolizumab 112
7.4.2.3 Infusion Interruptions/Delays/Withholding and Re-start in Case of Technical/Logistical Issues 112
7.4.2.4 Infusion Interruptions/Delays/Withholding and Re-start due to Adverse Events 114
7.4.3 Hepatotoxicity Stopping and Rechallenge Rules 131
7.5 Preparation/Handling/Storage/Accountability 131
7.6 Treatment Compliance 131
7.7 Treatment of Overdose 131
7.8 Prior and Concomitant Treatment 132
7.8.1 Prior Treatment 132
7.8.2 Concomitant Treatment 132
7.8.2.1 Supportive Care 133
7.8.2.2 Bone Disease Therapy 133
7.8.2.3 Growth Factors 133
7.8.2.4 Tumor Lysis Syndrome 133
7.8.2.5 Nausea, Vomiting, and Diarrhea 134
7.8.2.6 Vaccines 134

8. Discontinuation Criteria 135
8.1 Discontinuation of Study Treatment 135
8.2 Discontinuation From the Study 136
8.2.1 Reasons for Removal From Washout, Run-in, or Invasive Procedures 137
8.2.2 Reasons for Removal From Study 137
8.3 Lost to Follow-up 137

9. Study Assessments and Procedures 138
9.1 General Study Periods 138
9.1.1 Screening, Enrollment and/or Randomization 138
9.1.2 Treatment Period 138
9.1.3 Safety Follow-up 139
9.1.4 Long-term Follow-up 139
9.1.5 End of Study 139
9.2 Description of General Study Assessments and Procedures 139
9.2.1 General Assessments 139
9.2.1.1 Informed Consent 139
9.2.1.2 Demographics 139
9.2.1.3 Medical History 140
9.2.1.4 Physical Examination 140
9.2.1.5 Neurological Examination 140

[redacted]

[redacted]
9.2.1.8 Physical Measurements 141
9.2.1.9 Performance Status 141
9.2.2 Efficacy Assessments 141
9.2.3 Safety Assessments 142
9.2.3.1 Adverse Events 142
9.2.3.2 Vital Signs 146
9.2.3.3 Pulse Oximetry 148
9.2.3.4 Electrocardiograms 148
9.2.3.5 Vital Status 149
9.2.4 Clinical Laboratory Assessments 149
9.2.4.1 Pregnancy Testing 149
[redacted]
9.2.5 Pharmacokinetic Assessments 151
[redacted]
10. Statistical Considerations 155
10.1 Sample Size Determination 155
10.2 Analysis Sets, [redacted] and Covariates 156
10.2.1 Analysis Sets 156
10.2.2 Covariates 157
[redacted]
10.2.4 Handling of Missing and Incomplete Data 157
10.3 Adaptive Design 157
10.4 Statistical Analyses 158
10.4.1 Planned Analyses 158
10.4.1.1 Interim Analysis and Early Stopping Guidelines 158
10.4.1.2 Primary Analysis 160
10.4.1.3 Final Analysis 161
10.4.2 Methods of Analyses 161

10.4.2.1 General Considerations....161
10.4.2.2 Efficacy Analyses....161
10.4.2.3 Safety Analyses....161
10.4.2.4 Other Analyses....163

11. References....164

12. Appendices....168
12.1 Appendix 1. List of Abbreviations and Definitions of Terms....169
12.2 Appendix 2. Clinical Laboratory Tests....173



12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting....184
Definition of Disease-related Event....184
Definition of Adverse Event....184
Definition of Serious Adverse Event....186
Definition of Adverse Device Effect....186
Recording Adverse Events, Disease-related Events (if applicable), Serious Adverse Events, and Serious Disease-related Events (if applicable)....187
Evaluating Adverse Events and Serious Adverse Events....188
Reporting of Serious Adverse Event....190
12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy Information....196
Collection of Pregnancy Information....197
12.6 Appendix 6. Sample Storage and Destruction....199
12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines....201
Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity....201

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity....202
Drug-induced Liver Injury Reporting and Additional Assessments....202
12.8 Appendix 8. Operating Characteristic for 2-parameter BLRM Design....205
12.9 Appendix 9. Performance Status According to Eastern Cooperative Oncology Group (ECOG) Scale....209
12.10 Appendix 10. RECIST 1.1 With Prostate Cancer Working Group 3 (PCWG3) Modifications....210
12.11 Appendix 11. Expected Disease-related Events for Metastatic Castration-resistant Prostate Cancer....213
12.12 Appendix 12. Specific Guidance for Cytokine Release Syndrome....214
12.13 Appendix 13. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading....215
12.14 Appendix 14. Specific Guidance for Immune-effector Cell-associated Neurologic Syndrome....217
12.15 Appendix 15. Approximate Blood Volume Collection....220
12.16 Appendix 16. Modified Toxicity Probability Interval Design (mTPI-2)....221
12.17 Appendix 17. COVID-19 Guidance....223

List of Tables

Table 2-1. Schedule of Activities for C1D1 Extended IV Infusion (Cycle 1 Only) – Parts 1, 2, and 3....30
Table 2-2. Schedule of Activities (Cycle 2 and Beyond) – Parts 1, 2, and 3....35
[redacted]
Table 2-4. Part 6: Schedule of Activities (Cycle 1 Only)....45
Table 2-5. Part 6: Schedule of Activities (Cycle 2 and Beyond)....48
Table 2-6. Schedule of Pharmacokinetic Samples (All timepoints relative to AMG 160 dosing[e,f])....51
Table 2-7. Schedule of Imaging Assessments (Cycle Independent)....53
Table 2-8. Summary of Step Dosing and Extended IV Infusion Schemas (Cycle 1)....54
Table 3-1. Key Safety Risks for AMG 160....69
Table 3-2. Key Risks for Pembrolizumab....71
Table 3-3. Key Risks for Etanercept....73
Table 7-1. Study Treatment....93
[redacted]

[redacted]

Table 12-1. LOCAL Laboratory Analyte Listing 173
Table 12-2. CENTRAL Laboratory Analyte Listing 174
Table 12-3. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity 202
Table 12-4. True Probability of DLT by Scenario 206
Table 12-5. True Probability of DLT or Grade 2 Related Adverse Event by Scenario 206
Table 12-6. Probability by Planned Dose Level for Initiating Multiple Subject Cohorts by Scenario 207
Table 12-7. Operating Characteristics by Scenario 207
Table 12-8. The Rate of MTD Selected and the Number of Subjects Assigned at Each Dose Level by Scenario 208
Table 12-9. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome 215
Table 12-10. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading 216
Table 12-11. ASBMT Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults 218
Table 12-12. Assessment and Supportive Care Recommendations 219

[redacted]

Table 12-14. mTPI-2 Trial Monitoring Table 222

List of Figures

Figure 2-1. Parts 1, [redacted] Study Schema 25
Figure 2-2. Part 2 Study Schema 26
Figure 2-3. Part 3 Study Schema 27
Figure 2-4. Part 6 Study Schema 28

[redacted]

Figure 10-1. The Probability of Stopping at Futility 159

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form 191
Figure 12-2. Pregnancy Notification Form 198

1. Protocol Synopsis

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Short Protocol Title: A Phase 1 Study of AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Study Phase: 1

Indication: Metastatic castration-resistant prostate cancer (mCRPC)

Rationale

Part 1: AMG 160 Monotherapy

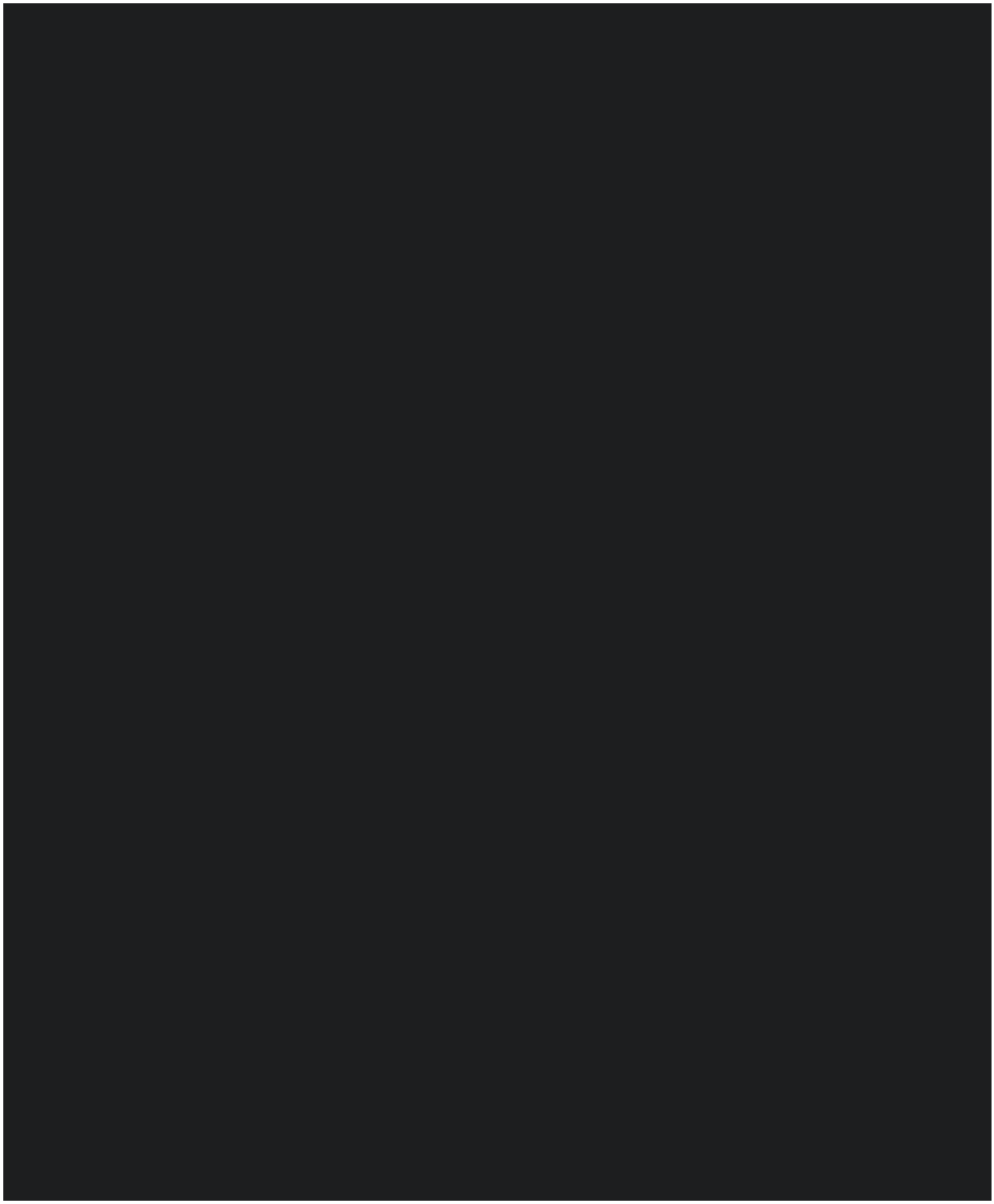
AMG 160 is a novel half-life extended (HLE) bispecific T-cell engager (BiTE®) molecule designed to direct T effector cells towards prostate-specific membrane antigen (PSMA)-expressing cells, with a single chain fragment crystallizable (scFc) moiety for extended half-life. Part 1 is a first-in-human study in adult subjects with mCRPC to assess AMG 160 safety and tolerability, pharmacokinetics (PK), and anti-tumor activity, with additional exploratory objectives to assess [redacted] Two separate dose expansion parts (1a and 1b) will be included into Part 1. Dose expansion 1a will enroll approximately 50 subjects, independent of PSMA status. Dose expansion 1b will enroll approximately 50 subjects [redacted].

Part 2: AMG 160 Combination with Pembrolizumab

It has been shown that the BiTE molecule mode of action leads to an upregulation of immune checkpoints, such as PD-1 on immune cells and PD-L1 on tumor cells, and that the combination of the BiTE molecule blinatumomab with the PD-1 inhibitor nivolumab is safe and tolerable in subjects with acute lymphoblastic leukemia (ALL) with evidence of antitumor activity (Kobold et al 2018; Webster et al, 2018). Part 2 of the study will evaluate the safety and tolerability of AMG 160 given in combination with the PD-1 inhibitor pembrolizumab with additional objectives to explore PK, pharmacodynamics (PD), immunogenicity, and anti-tumor activity of AMG 160 when given in combination with pembrolizumab.

Part 3: Etanercept Prophylaxis for AMG 160-related CRS

Cytokine release syndrome (CRS) is an identified safety risk for AMG 160 and symptoms of CRS are partly mediated by the cytokine tumor necrosis factor alpha (TNF-α; Lee et al, 2014; Grupp et al, 2013). Recent preclinical and clinical studies involving cluster of differentiation (CD)3 bispecific immunotherapies with similar mechanisms of action as AMG 160 have reported that pretreatment with TNF-α inhibitors may mitigate CRS without affecting antitumor activity (Li et al, 2019; Lee at al, 2014; Grupp et al, 2013; Lin et al, 2006). Part 3 will evaluate whether prophylaxis with the TNF-α inhibitor etanercept will decrease the frequency and severity of CRS without compromising the efficacy of AMG 160. If proven successful, etanercept and/or dexamethasone may be included in Parts 1 and [redacted]



Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

Elevated cytokines following AMG 160 administration may suppress CYP enzyme activity which may alter plasma concentrations of concomitant drugs that are metabolized via CYP mediated pathway. Therefore, Part 6 of this study will evaluate the effect of AMG 160 on plasma exposures of specific probes of CYP enzymes using a modified Cooperstown 5+1 CYP phenotyping cocktail.

Objectives/Endpoints

Parts 1, 3 [redacted] and 6: AMG 160 monotherapy	
Objectives	**Endpoints**
Primary	
• Evaluate the safety and tolerability of AMG 160 in adult subjects • **Part 1 only:** Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)	• dose-limiting toxicities (DLTs) • treatment-emergent adverse events • treatment-related adverse events • changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 160	• PK parameters for AMG 160 following intravenous (IV) administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate preliminary anti-tumor activity of AMG 160	• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%) • duration of response (DOR) (per RECIST 1.1) • PSA DOR based on PSA50 response • ^{68}Gallium (^{68}Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography(PET)/computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) PET/CT based response evaluation (Parts [redacted], and 6 are not included) • time to progression (radiographic and PSA) • progression-free survival (PFS) (radiographic and PSA) • 1, 2, and 3-year overall survival (OS) • circulating tumor cells (CTCs) – response (CTC0) and rate of CTC conversion • other Prostate Cancer Working Group 3 (PCWG3)-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)
• Part 6 only: Evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma	• PK parameters of specific probes of CYP enzymes including, but not limited to, C_{max}, area under the concentration-time curve over a 24-hour period (AUC24) and, if feasible, $t_{1/2}$

exposures of specific probes of CYP enzymes	
Part 2: AMG 160 in combination with pembrolizumab	
Objectives	**Endpoints**
Primary	
• Evaluate the safety and tolerability of AMG 160 in combination with pembrolizumab in adult subjects • Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of AMG 160 in combination with pembrolizumab	• dose-limiting toxicities (DLTs) • treatment-emergent adverse events • treatment-related adverse events • changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 160 in combination with pembrolizumab	• PK parameters for AMG 160 following intravenous (IV) administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate preliminary anti-tumor activity of AMG 160 in combination with pembrolizumab	• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%) • duration of response (DOR) (per RECIST 1.1) • PSA DOR based on PSA50 response • ^{68}Ga-PSMA-11 PET/ CT and ^{18}F-FDG PET/CT based response evaluation • time to progression (radiographic and PSA) • progression-free survival (PFS) (radiographic and PSA) • 1, 2, and 3-year overall survival (OS) • circulating tumor cells (CTCs) – response (CTC0) and CTC conversion • other PCWG3-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)

Hypothesis

AMG 160 monotherapy and in combination with pembrolizumab will demonstrate acceptable safety and tolerability in subjects with mCRPC at 1 or more dose levels with

at least 1 dose level showing preliminary evidence of anti-tumor activity. No formal hypotheses will be tested.

Overall Design

Part 1: AMG 160 Monotherapy

Part 1 is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 160 administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks (Q2W) in a 28-day cycle in subjects with mCRPC (up to 190 subjects; Figure 2-1). To reduce the incidence of CRS, the cycle 1 dosing schedule may be adapted to include an alternate dosing schedule involving a planned 3-day eIV infusion (with the option to modify to range from 2-day to 7-day infusion) within the first week of cycle 1 followed by target doses (short-term IV infusions).

The study will consist of:

- dose-exploration phase
- dose-expansion phase (1a and 1b)

The dose-exploration phase of the study will estimate the MTD of AMG 160 using a Bayesian logistic regression model (BLRM). A RP2D may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.

Following the dose-exploration phase in Part 1, a dose-expansion phase will be conducted in 2 parts (1a and 1b) to confirm safety, PK, and pharmacodynamics at the MTD or RP2D and to obtain further safety and efficacy data [redacted] analysis. Dose expansion 1a will enroll approximately 50 subjects, independent of PSMA status. Dose expansion 1b will enroll approximately 50 subjects [redacted]

During the dose exploration phase, individual cohorts of subjects from [redacted] will be enrolled with a safety lead-in at 1 or more dose levels below the MTD or RP2D followed by evaluation at the MTD or RP2D to confirm the safety, tolerability, MTD and/or RP2D of AMG 160 in [redacted] subjects, respectively.

Additional subjects (up to 20) may be enrolled in 1 or more monotherapy dose levels that have been shown to be safe and tolerable (defined as backfill enrollment). This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and pharmacodynamics of AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

Part 2: AMG 160 Combination with Pembrolizumab

This combination dose exploration study will explore the safety, **PK**, and efficacy of AMG 160 in combination with the PD-1 inhibitor pembrolizumab in approximately **3**0 subjects with mCRPC (Figure 2-2).

AMG 160 will be administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC. The starting dose of AMG 160 will be 1 dose level below the dose level that has been recommended as safe and tolerable by Dose Level Review Team (DLRT) at the time Part 2 is initiated. To reduce the incidence of CRS, the cycle 1 dosing schedule includes multi-step and/or eIV infusion dosing schedule (see Section 7.1.1.1) as per the recommendation of the DLRT. [redacted] pembrolizumab infusion will take place after AMG 160

infusion and post-infusion flush. The DLRT may modify the AMG 160 and pembrolizumab dosing schedule based on emerging safety data.

This dose exploration study will estimate the MTD and/or RP2D of AMG 160 in combination with pembrolizumab using a modified toxicity probability interval design (mTPI-2; Section 12.16). Recommended phase 2 dose may be identified based on emerging safety, efficacy, pharmacokinetic, and pharmacodynamic data prior to reaching an MTD. If necessary, 10 additional subjects may be enrolled at the RP2D for subjects in order to obtain additional safety and pharmacokinetic data. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.

Part 3: Etanercept Prophylaxis for AMG 160-related CRS

Part 3 will evaluate the effect of etanercept premedication on the safety, tolerability, and efficacy of AMG 160. Specifically, Part 3 will assess whether prophylaxis with the TNF-α inhibitor etanercept might decrease the frequency and severity of CRS without compromising the efficacy of AMG 160.

In an initial cohort of 6 to 8 subjects, AMG 160 will be administered as described in Part 1 at the MTD, RP2D, or highest dose level deemed safe and tolerable (Figure 2-3). In addition to dexamethasone prophylaxis, subjects in the cohort will also receive prophylaxis with etanercept [redacted] prior to each cycle 1 dose of AMG 160.

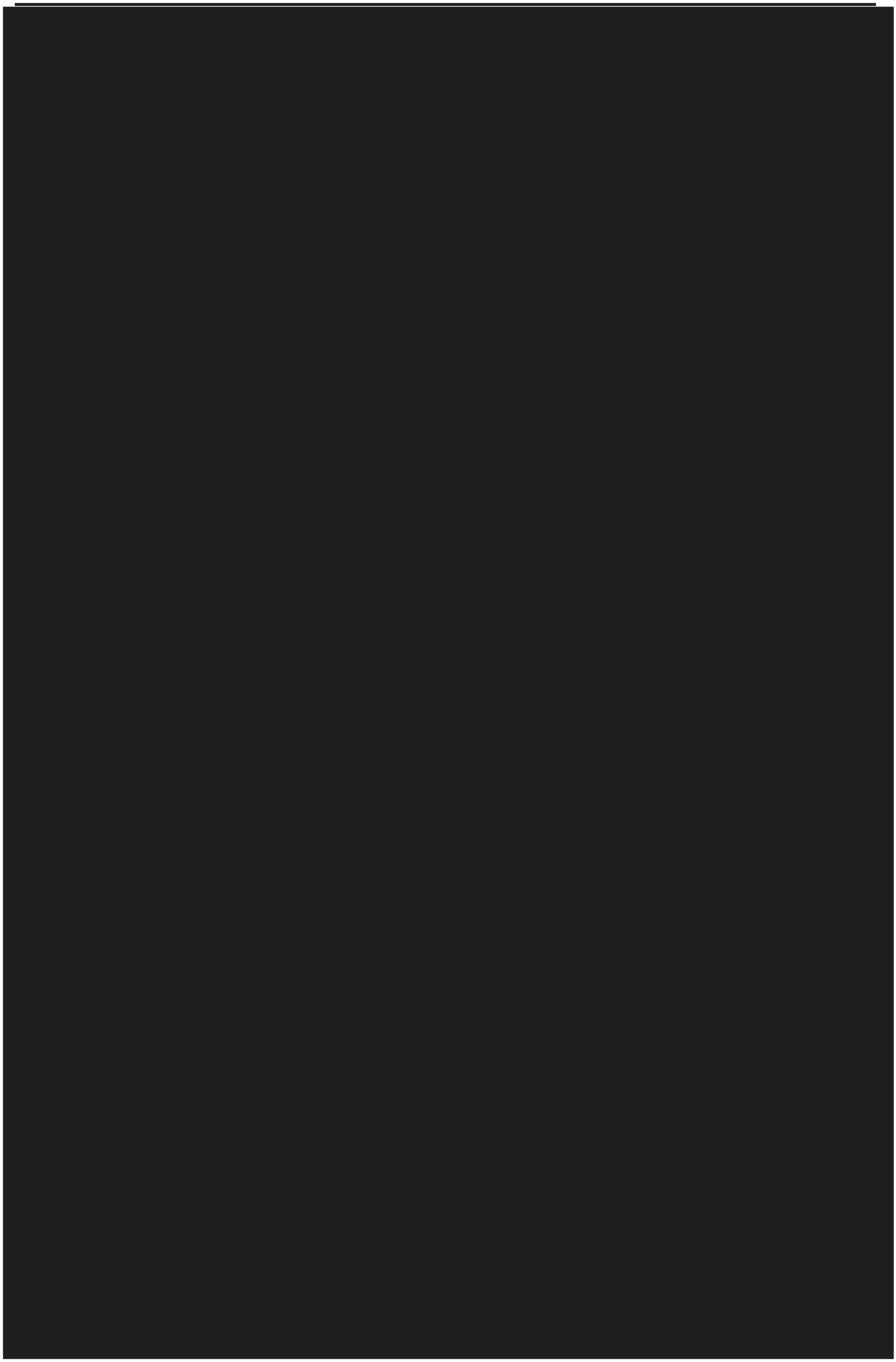
Subject incidence of safety events, including dose-limiting toxicities (DLTs), serious adverse events, and adverse events leading to treatment discontinuation or dose reduction, will be reviewed when at least 3 DLT-evaluable subjects complete the DLT window. If etanercept does not reduce the signs and symptoms of CRS in the initial cohort of 6 to 8 subjects, enrollment in Part 3 will be discontinued.

If etanercept prophylaxis reduces signs and symptoms of CRS and improves tolerability of AMG 160 in cohort 1, an additional cohort of 6-8 subjects may receive AMG 160 with etanercept prophylaxis only (ie, without dexamethasone premedication) [redacted] prior to each cycle 1 doses of AMG 160. Based on safety data, additional subjects (up to 20 in the cohort) may be enrolled in Part 3 to evaluate the effect of etanercept premedication (with or without dexamethasone premedication) on the safety, tolerability, and efficacy of AMG 160.

If etanercept reduces signs and symptoms of CRS without impacting efficacy in Part 3, etanercept prophylaxis (with or without dexamethasone prophylaxis) may be added to Parts 1, 2, [redacted]

Part 3 will be conducted in US and Canada only.

[redacted]



Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

Part 6 of this study will evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma exposures of specific probes of CYP enzymes using a modified Cooperstown 5+1 CYP phenotyping cocktail. Up to 8 subjects are planned to be enrolled. Briefly, each subject will receive a single oral dose of all components of the CYP phenotyping cocktail one day prior to cycle 1 day 1 and subsequently on cycle 2 day 1. AMG 160 will be administered at the MTD/RP2D as determined in Part 1.

Part 6 will be conducted in **the** US and Singapore.

Number of Subjects

Approximately 218 to 288 subjects will be enrolled in US, Canada, Asia, Europe, and Australia in this study.

	Number of Subjects		
Study Part	Total	Subsets	
Part 1: AMG 160 monotherapy	120-190	Dose exploration	70-90
		Step-dosing	30
		eIV	20
		[redacted]	
		Backfill (optional)	20
		Dose expansion	100
		Expansion 1a	50
		Expansion 1b	50
Part 2: AMG 160 in combination with pembrolizumab	30		
Part 3: Etanercept prophylaxis for AMG 160-related CRS	20		
[redacted]			
Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort	8		
Total	218-288		

Summary of Subject Eligibility Criteria

All Parts:

Key Inclusion Criteria:

- Subjects with histologically or cytologically confirmed mCRPC who are refractory to a novel antiandrogen therapy (abiraterone, enzalutamide, and/or apalutamide) and have failed at least 1 (but not more than 2) taxane regimens (or who are deemed medically unsuitable to be treated with a taxane regimen or have actively refused treatment with a taxane regimen). Progression on novel antiandrogen therapy may have occurred in the non-metastatic CRPC setting.



- Subjects must have undergone bilateral orchiectomy or must be on continuous ADT with a gonadotropin-releasing hormone (GnRH) agonist or antagonist
- Total serum testosterone ≤ 50 ng/dL or 1.7 nmol/L
- Evidence of progressive disease, defined as 1 or more PCWG3 criteria:
  - PSA level ≥ 1 ng/mL that has increased on at least 2 successive occasions at least 1 week apart
  - nodal or visceral progression as defined by RECIST 1.1 with PCGW3 modifications
  - appearance of 2 or more new lesions in bone scan

Key Exclusion Criteria:

- Any anticancer therapy or immunotherapy within 4 weeks of start of first dose, not including luteinizing hormone-releasing hormone agonist (LHRH)/GnRH analogue (agonist/antagonist). Subjects on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization are eligible
- Prior PSMA-targeted therapy (subjects on prior PSMA radionuclide therapy may be eligible if discussed with Amgen medical monitor prior to enrollment)
- Central nervous system (CNS) metastases, leptomeningeal disease, or spinal cord compression
- Active autoimmune disease or any other diseases requiring immunosuppressive therapy while on study
- Needing chronic systemic corticosteroid therapy (prednisone dose > 10 mg per day or equivalent) or any other immunosuppressive therapies (including anti-tumor necrosis factor alpha [TNFα] therapies) unless stopped 7 days prior to start of dosing
- For Part 2 only:
  - Age ≥ 75 years at the time of signing the informed consent (EU only)

- Subjects on a prior PD-1 or PD-L1 inhibitor who experienced a grade 3 or higher immune-related adverse event prior to first day of dosing
- History or evidence of interstitial lung disease or active, non-infectious pneumonitis

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

All Parts:

Investigational product (AMG 160) will be administered as an eIV infusion dosing involving a first step dose administered via a planned 3-day eIV infusion (with the option to modify to range from 2-day to 7-day infusion) beginning on cycle 1 day 1, followed by the target dose (60-minute IV infusions) on days 8 and 22 (28-day cycle + 7-day infusion-free interval [days 29-35]; see Table 2-1). After cycle 1, AMG 160 will be administered every 2 weeks in 28-day cycles on days 1 and 15.

To reduce the potential of CRS, the dosing schedule may be adapted to include 1 or more of the following measures, as per DLRT recommendation based on emerging safety data:

- Prophylaxis with IV hydration (eg, 1 L normal saline), corticosteroids (eg, dexamethasone 8 mg), acetaminophen (eg, 975 mg PO single dose) and/or tocilizumab (4-8 mg/kg IV single dose) **(or siltuximab if tocilizumab is not available)** prior to or immediately after AMG 160 doses in cycle 1 and beyond.

Premedication

- Dexamethasone 8 mg PO (or equivalent dose of other corticosteroids) will be administered 6-16 hours prior to all doses of AMG 160 in cycle 1. Additionally, dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all doses of AMG 160 in cycle 1. [redacted]
- Per investigator discretion, prophylactic IV hydration (eg, 1 liter normal saline administered over 4-5 hours) should be given in cycle 1:
  - immediately after AMG 160 short-term (60 minute) infusions
  - after the start of C1D1 eIV infusion on day 1 on a different IV line

The DLRT may modify the premedication dosing regimen based on emerging safety data.

Part 2 only: AMG 160 in Combination With Pembrolizumab

AMG 160 and premedications (corticosteroids, IV fluids) will be dosed in the same way in all parts. The starting dose for AMG 160 will be 1 dose level below the dose that is deemed to be safe and well tolerated in Part 1.

[redacted]

Part 3 only: Etanercept Prophylaxis for AMG 160-related CRS

AMG 160 and premedications (corticosteroids, IV fluids) will be dosed in the same way in all parts. Additionally, etanercept [redacted] prior to all cycle 1 doses of AMG 160 in a cohort of 6 to 8 subjects. If the addition of etanercept reduces signs and symptoms of CRS, an additional cohort of 6 to 8 subjects may receive AMG 160 with etanercept prophylaxis only (ie, without dexamethasone premedication). Based on safety data, additional subjects (up to 20 in the cohort) may be enrolled in Part 3 with etanercept premedication (with or without dexamethasone premedication).

[redacted]

Procedures

After written informed consent has been obtained, all screening tests and procedures will be performed within 28 days prior to cycle 1 day 1 dosing, unless otherwise noted. Serial clinical safety and study evaluations as per the Schedule of Activities will be performed including physical examination, vital signs, clinical laboratory tests, radiological assessment [redacted] PK, and [redacted] sample collections. All subjects in Parts 1, 2, and 3 will receive baseline screening by ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT before dosing.

Parts 1, 2, 3, and 6: All subjects will be hospitalized for intensive monitoring for at least 48 hours post AMG 160 infusion during the first cycle. Subjects in the eIV cohort will be hospitalized during infusion days of the first week of treatment (ie, 3-day hospitalization for 3-day eIV). The subjects may be discharged after the 48-hour period if there are no

clinically significant symptoms of CRS or other acute toxicities. Minimum hospitalization times for subjects are described in detail in Table 7-1.

[redacted]

All parts: Routine radiological imaging (CT/ magnetic resonance imaging [MRI]) and tumor burden assessments will be performed as outlined in the Schedule of Activities. Assessment of disease response will be determined based on PSA, CTCs, and RECIST 1.1 guidelines with PCWG3 modifications for patients with measurable disease.

To further assess the risk of delayed adverse events, the subject must return for safety follow-up visit at least 30 (+ 3) days after the last dose of AMG 160. Long-term follow-up will be conducted every 6 months up to 3 years from the first dose of AMG 160 for all subjects who have not withdrawn consent by clinic visit, telephone or chart review to assess for survival and/or the commencement of subsequent cancer therapy.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Section 2.2.

Statistical Considerations

All subjects who are enrolled and receive at least 1 dose of AMG 160 or pembrolizumab will be included in the analysis, unless otherwise specified. A formal interim analysis of available safety and efficacy data will occur when all remaining dose-escalation subjects have had the opportunity to complete 28 days on study for Part 1. A similar interim analysis will be conducted for Part 2 when all remaining subjects have had the opportunity to complete 28 days on the study. This interim analysis will estimate the MTD (MTD1, MTD2, MTD3, and/or MTD4, as applicable if step-dosing is implemented), support the determination of the RP2D, and support the evaluation of benefit/risk profile of AMG 160 as monotherapy and in combination with pembrolizumab. [redacted] The primary analysis will occur when target enrollment is complete for Part 1 dose exploration ([redacted]) and Part 1 dose-expansion cohort 1a and each subject has the opportunity to receive 6 months of treatment. The final analysis will occur when target enrollment is complete for all parts and all subjects have ended the study.

Descriptive statistics will be provided for selected demographics, safety, PK, pharmacodynamic (PD), [redacted] data by treatment (monotherapy vs combination with pembrolizumab) 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 number and percentage of subjects reporting any treatment-emergent adverse events, treatment-related adverse events, and disease-related events will be tabulated. Clinical laboratory tests, ECG, physical examination findings, and vital sign data will be listed. Depending on the size and scope of changes, summaries of above safety parameters and/or changes from baseline over time may be provided.

The objective response rate with corresponding exact 95% CIs will be calculated using the Clopper-Person method and tabulated for subjects treated at the MTD/RP2D by treatment (monotherapy vs combination with pembrolizumab).

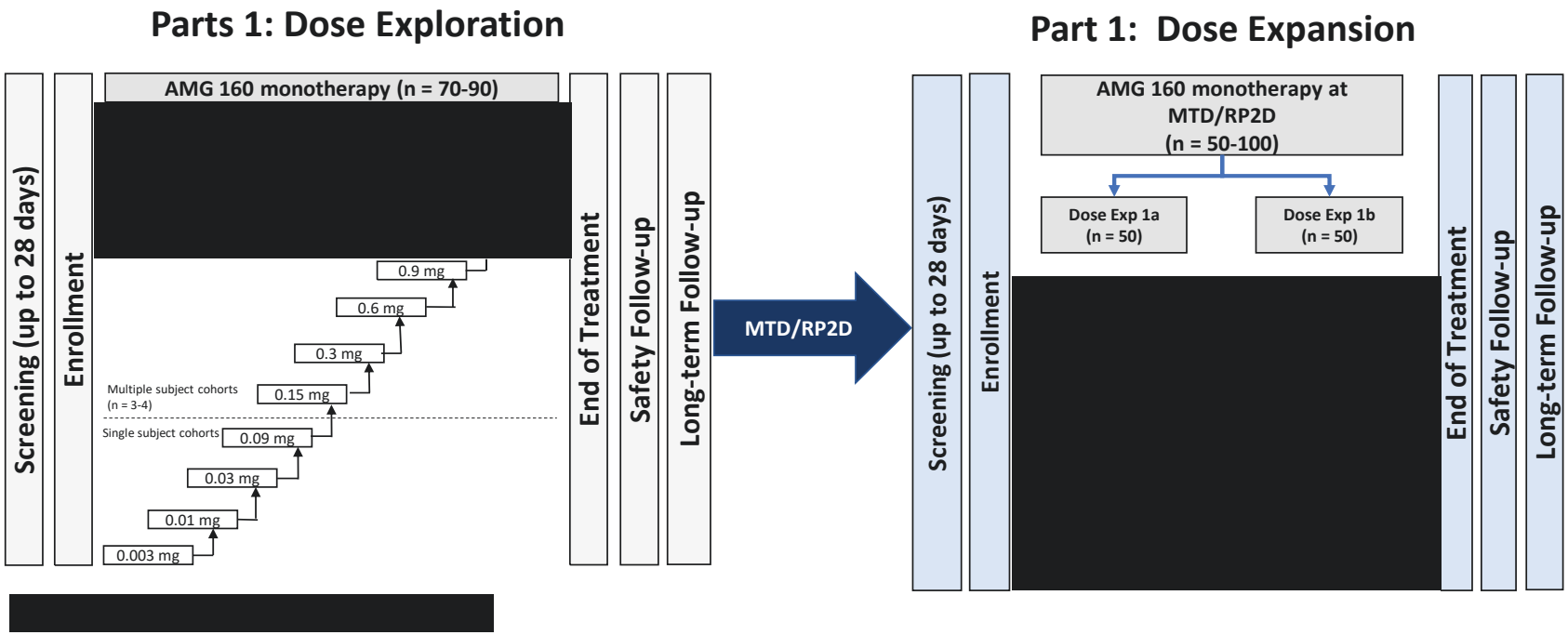
For a full description of statistical analysis methods, please refer to Section 10 and Sections 12.8 and 12.16.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Parts 1, [redacted] Study Schema



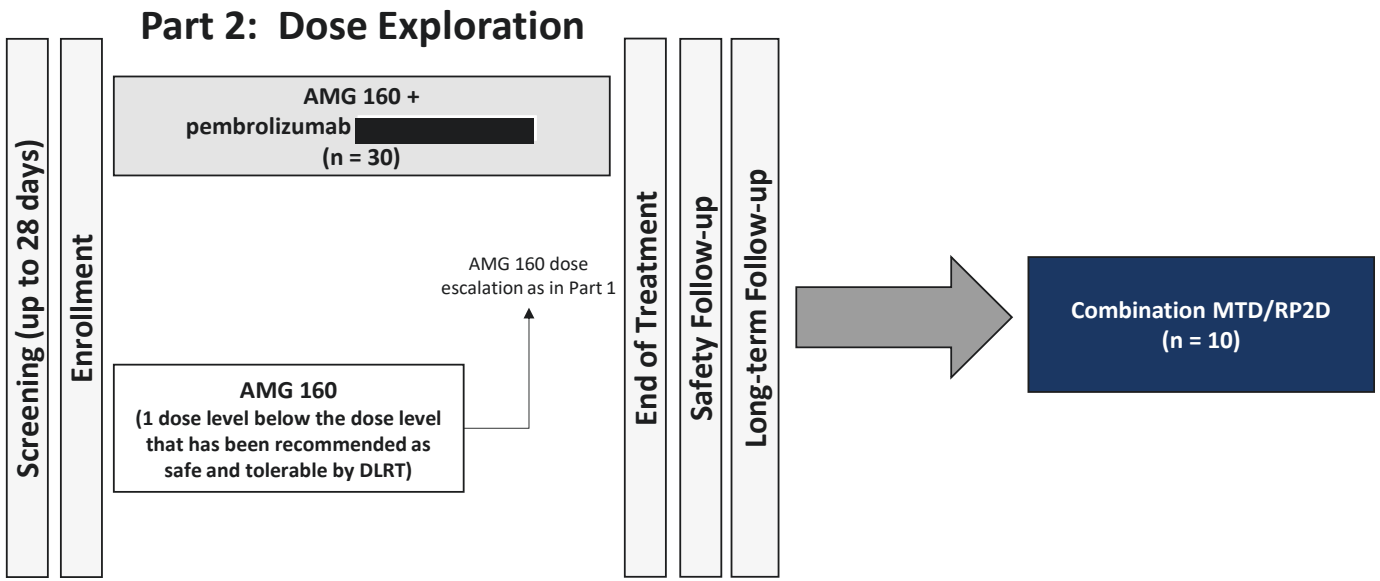
[redacted]

MTD = maximum tolerated dose; RP2D = recommended phase 2 dose

Study Periods:

- Screening: up to 28 days before enrollment
- Treatment: AMG 160 administered IV every 2 weeks (cycle 1 exception for extended IV infusion); treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines)
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product
- Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first
- Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent

Figure 2-2. Part 2 Study Schema

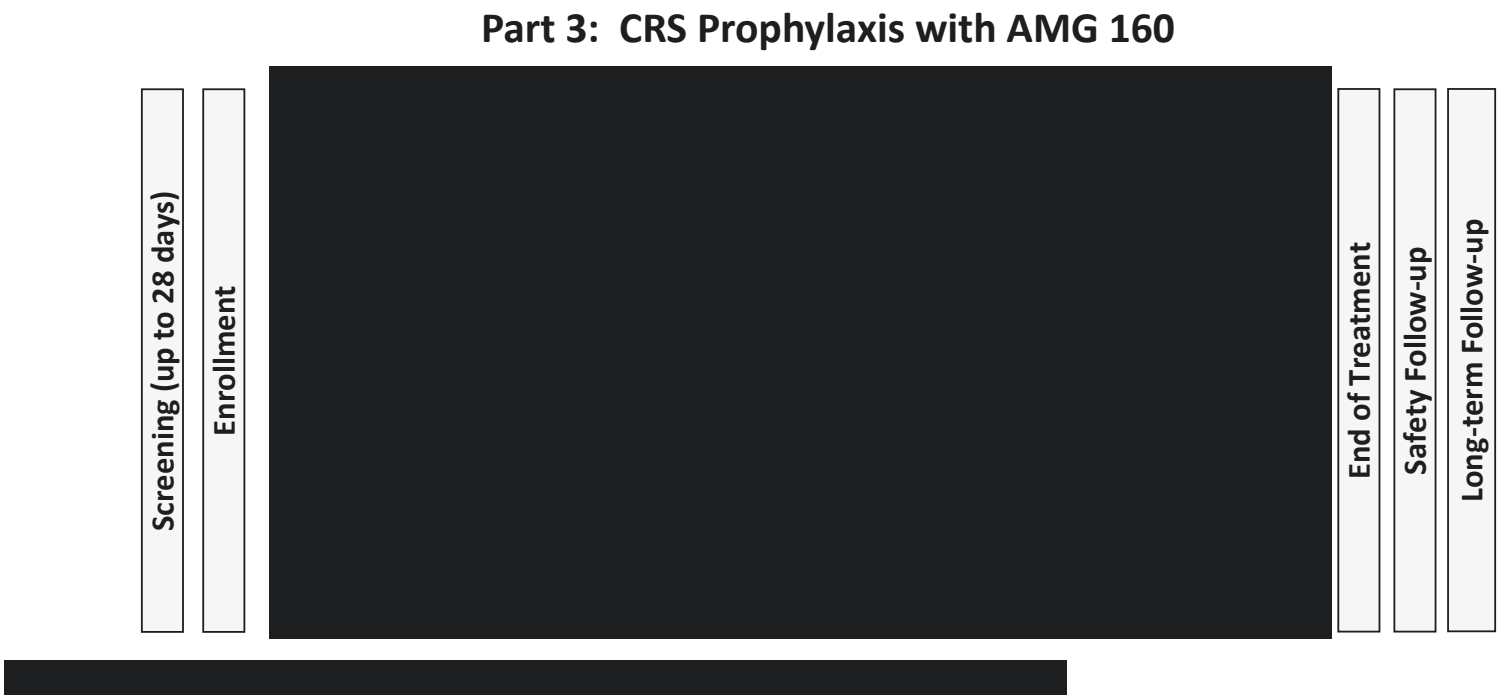


DLRT = Dose Level Review Team; [redacted]; MTD = maximum tolerated dose; [redacted]; RP2D = recommended phase 2 dose

Study Periods:

- Screening: up to 28 days before enrollment
- Treatment: AMG 160 administered IV every 2 weeks (except if step-dosing or extended IV infusion is implemented in cycle 1); pembrolizumab [redacted] treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines)
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product
- Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first
- Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent

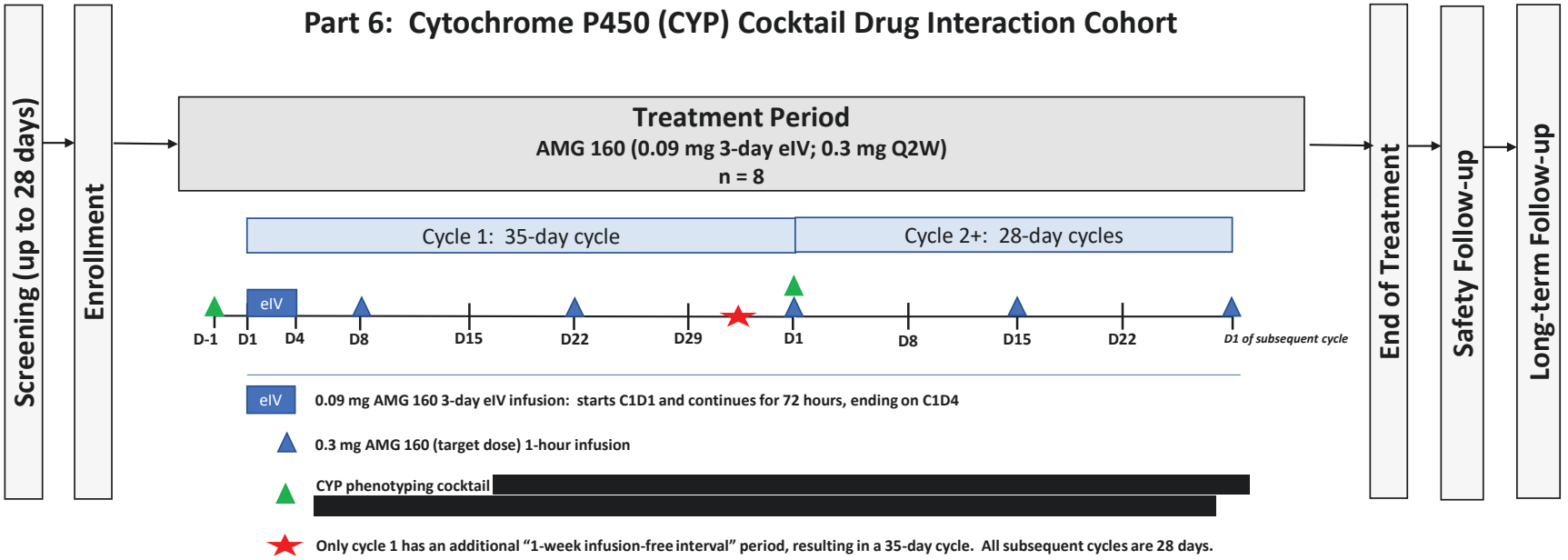
Figure 2-3. Part 3 Study Schema



Study Periods:

- **Screening: up to 28 days before enrollment**
- **Treatment: AMG 160 administered IV every 2 weeks (cycle 1 exception for step-dosing or extended IV infusion); treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines)**
- **End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product**
- **Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first**
- **Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent**

Figure 2-4. Part 6 Study Schema



C1D1 = cycle 1 day 1; eIV = extended intravenous; PCWG3 = Prostate Cancer Working Group 3; Q2W = every 2 weeks

Study Periods:

- Screening: up to 28 days before enrollment
- Treatment: AMG 160 administered IV every 2 weeks (cycle 1 exception for extended IV infusion); treatment continues until progression (treatment beyond disease progression may be allowed as per PCWG3 guidelines). CYP phenotyping cocktail to be administered one day prior to cycle 1 day 1 (~24 hours prior to AMG 160 infusion) and on cycle 2 day 1 (immediately after AMG 160 infusion).
- End of treatment: should occur as soon as possible (within 14 days) after the last dose of investigational product
- Safety follow-up: approximately 30 (+3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first
- Long-term follow-up: every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent

2.2 Schedule of Activities

Quick link to SoA	Table Title
Table 2-1	Schedule of Activities for C1D1 Extended IV Infusion (Cycle 1 Only) – Parts 1, 2, and 3
Table 2-2	Schedule of Activities (Cycle 2 and Beyond) – Parts 1, 2, and 3
[redacted]	
Table 2-4	Part 6: Schedule of Activities (Cycle 1 Only)
Table 2-5	Part 6: Schedule of Activities (Cycle 2 and Beyond)
Table 2-6	Schedule of Pharmacokinetic Samples – All Parts [redacted]
Table 2-7	Schedule of Imaging Assessments (Cycle Independent)
Table 2-8	Summary of Step Dosing and Extended IV Infusion Schemas (Cycle 1)

Table 2-1. Schedule of Activities for C1D1 Extended IV Infusion (Cycle 1 Only) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]															Infusion-free interval	Notes
Week[c]		1						2			3			4			5	
Day[c]		1	2	3	4	5	6	8	9	10	15	19	20	22	23	24	29	
GENERAL / SAFETY ASSESSMENTS																		
Informed consent	X																	
Clinical evaluation	(X)	X	X	X	X	X*	X*	X	X	X	X	X		X	X	X	X	Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (see Section 9.2). (X): Additionally at screening: demographics, medical history, and height. X*: Only if 5-day eIV administered
Vital signs, pulse ox	X	(X)		X	X	X*	X*	(X)		X	X	X		(X)		X	X	(X): Refer to Section 9.2.3.2 for detailed vital sign collection time points. X*: Only if 5-day eIV administered
Part 1 only: 12-lead ECG (triplicate)		X			X*									X				Collected pre-infusion only on day 1 (baseline) and after EOI for remaining time points. X*: Collected EOI on day 4 for 3-day eIV and day 6 for 5-day eIV
Part 1 only: 12-lead ECG (single)	X																	
Parts 2-3: 12-lead ECG (single)	X	X			X*									X				Collected pre-infusion and after end of infusion. X*: Collected EOI on day 4 for 3-day eIV and day 6 for 5-day eIV.
[redacted]																		
ECHO or MUGA scan	X																	
AE/DRE Review	(X)	Continually throughout study																(X): Only if related to study-mandated procedures
SAE Review	Continually throughout study																	

Abbreviations and footnotes defined on last page of table.

Table 2-1. Schedule of Activities for C1D1 Extended IV Infusion (Cycle 1 Only) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]															Infusion-free interval	Notes
Week[c]		1						2			3			4			5	
Day[c]		1	2	3	4	5	6	8	9	10	15	19	20	22	23	24	29	
GENERAL / SAFETY ASSESSMENTS (continued)																		
Prior/concomitant medication	Continually throughout study																	See Section 7.6; includes review of patient diary for protocol-required therapies administered at home ([redacted]
LOCAL LABORATORY TESTING																		
CBC with differential	X	X	X	X	X			X	X	X	X	X		X	X	X	X	Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated. Blood samples must not be collected until at least 24 hours after PSMA or FDG PET scans.
Coagulation	X	X	X		X			X	X		X	X		X	X			
Chemistry panel	X	X	X	X	X			X	X	X	X	X		X	X	X	X	
Urinalysis	X																	
Testosterone	X																	
CENTRAL LABORATORY TESTS																		
[redacted]																		
PSA		X																Also collected locally. Additional unscheduled PSA measurements collected outside of this time point can be reported.
LDH, ALP		X																
Urine N-telopeptide		X																
[redacted]																		

Abbreviations and footnotes defined on last page of table.

Table 2-1. Schedule of Activities for C1D1 Extended IV Infusion (Cycle 1 Only) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]														Infusion-free interval	Notes
Week[c]		1						2			3			4			5	
Day[c]		1	2	3	4	5	6	8	9	10	15	19	20	22	23	24	29	
CENTRAL LABORATORY TESTS (continued)																		
[redacted]																		
PK sample collection		(X)																(X): See for Table 2-6 detailed AMG 160 PK (and in Part 2, pembrolizumab PK) collection schedule during treatment period.
[redacted]																		

Abbreviations and footnotes defined on last page of table.

Table 2-1. Schedule of Activities for C1D1 Extended IV Infusion (Cycle 1 Only) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]															Infusion-free interval	Notes
Week[c]		1						2			3			4			5	
Day[c]		1	2	3	4	5	6	8	9	10	15	19	20	22	23	24	29	
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES																		
Imaging	(X)																	(X): See Table 2-7 – assessments are cycle independent
Premedication		X						X						X				Refer to Section 7.1.4 for details.
AMG 160 3-day eIV infusion		X						X						X				
AMG 160 5-day eIV infusion		X						X						X				
Part 2 only: pembrolizumab								X										See Table 2-8 for overview of pembrolizumab administration.
Part 3 only: etanercept	(X)						X						X					(X): [redacted] prior to first dose of AMG 160.
3-day eIV hospitalization/ monitoring		X						X						X				See Table 7-1 for additional guidance regarding hospitalization. For C1D1 3-day eIV dosing, hospitalization beyond 72 hours may be allowed per investigator discretion.
5-day eIV hospitalization/ monitoring		X						X						X				See Table 7-1 for additional guidance regarding hospitalization. For C1D1 5-day eIV dosing, hospitalization beyond 5 days may be allowed per investigator discretion.

NOTE: This schedule of activities only applies to cycle 1. After cycle 1 day 28, there is a 1-week infusion-free interval. Then resume **Table 2-2** Schedule of Activities beginning in cycle 2.

AE = adverse event; ALP = alkaline phosphatase; [redacted] C1D1 = cycle 1 day 1; CBC = complete blood count; CTCs = circulating tumor cells; [redacted] DRE = disease-related event; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eIV = extended intravenous; [redacted] **FDG = fluorodeoxyglucose;** HLA = human leukocyte antigen; IPIM = Investigational Product Instruction Manual; IV = intravenous; LDH = lactate dehydrogenase; MUGA scan = multigated acquisition scan; **PET = positron emission tomography;** PG = pharmacogenomic; PK = pharmacokinetic; PO = orally; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; QD = once daily; SAE = serious adverse event; SCR = screening

[a] All screening procedures should be performed within 28 days prior to cycle 1 day 1 dosing.

[b] All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion (EOI) assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[c] Each visit week and day is relative to day 1 of each cycle. Cycle 1 visits have a ± 1-day window from designated time point unless otherwise specified.

[redacted]

Table 2-2. Schedule of Activities (Cycle 2 and Beyond) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	Cycle 2[a]										Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	
Week[e]	1			2		3			4		1	3				
Day[e]	1	2	3	8	12	15	16	17	22	26	1	15				Notes
GENERAL / SAFETY ASSESSMENTS																
Clinical evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (if indicated) (as described in Section 9.2).
Vital signs, pulse ox	(X)		X	X	X	(X)		X	X	X	X	X	X	X		(X): Refer to Section 9.2.3.2 for detailed vital sign collection time points
Part 1 only: 12-lead ECG (triplicate)	X					X										Collected post-infusion of AMG 160.
Part 1 only: 12-lead ECG (single)											(X)	(X)				(X): Cycles 3 and 4 only
Parts 2-3: 12-lead ECG (single)	X					X					(X)	(X)				Collected pre- and post-infusion of AMG 160. (X): Cycles 3 and 4 only
[redacted]																
AE/DRE review	Continually throughout study															
SAE review	Continually throughout study															
Prior/concomitant medication	Continually throughout study															See Section 7.6; includes review of patient diary for protocol-required therapies administered at home [redacted]
Survival status and/or subsequent cancer therapy															X	

Abbreviations and footnotes defined on last page of table.

Table 2-2. Schedule of Activities (Cycle 2 and Beyond) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	Cycle 2[a]										Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	Notes
Week[e]	1			2		3			4		1	3				
Day[e]	1	2	3	8	12	15	16	17	22	26	1	15				
LOCAL LABORATORY TESTS																
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Blood samples must not be collected until at least 24 hours after PSMA or FDG PET scans.
Coagulation	X		X	X	X		X		X	X	X	X	X	X		
Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Blood samples must not be collected until at least 24 hours after PSMA or FDG PET scans.
Urinalysis	X										(X)					(X): Collected D1 of every other cycle (C2, C4, C6, etc.)
CENTRAL LABORATORY TESTS																
[redacted]																
PSA	X										X		X	X		Also collected locally. Additional unscheduled PSA measurements collected outside of these time points can be reported.
LDH, ALP	X										X		X			
Urine N-telopeptide	X										X		X			
[redacted]																

Abbreviations and footnotes defined on last page of table.

Table 2-2. Schedule of Activities (Cycle 2 and Beyond) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	Cycle 2[a]										Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	
Week[e]	1			2		3			4		1	3				
Day[e]	1	2	3	8	12	15	16	17	22	26	1	15				Notes
CENTRAL LABORATORY TESTS (continued)																
[redacted]																
PK sample collection	(X)															(X): See for Table 2-6 detailed AMG 160 PK collection schedule during treatment period.
[redacted]																

Abbreviations and footnotes defined on last page of table.

Table 2-2. Schedule of Activities (Cycle 2 and Beyond) – Parts 1, 2, and 3

Study Period/ Treatment Cycle	Cycle 2[a]										Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	
Week[e]	1			2		3			4		1	3				
Day[e]	1	2	3	8	12	15	16	17	22	26	1	15				Notes
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES																
Imaging	(X)															(X): See Table 2-7 – assessments are cycle independent
Premedication	X					X										Refer to Section 7.1.4 for details.
AMG 160 IV infusion	X					X					X	X				
Part 2 only: pembrolizumab	X										X					See Table 2-8 for overview of pembrolizumab administration.

[redacted] AE = adverse event; ALP = alkaline phosphatase; ANA = antinuclear antibodies; ANCA = antineutrophil cytoplasmic antibodies; [redacted] C = cycle; CBC = complete blood count; CTCs = circulating tumor cells; [redacted] D = day; DRE = disease-related event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; [redacted] **FDG = fluorodeoxyglucose;** IPIM = Investigational Product Instruction Manual; IV = intravenous; LDH = lactate dehydrogenase; LTFU = long-term follow-up; PBMC = peripheral blood mononuclear cell; **PET = positron emission tomography;** PK = pharmacokinetic; PO = orally; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; QD = once daily; SAE = serious adverse event; SCR = screening; SFU = safety follow-up

[a] Please follow Table 2-1 for the procedures/activities for cycle 1 and Table 2-2 for cycle 2 and subsequent cycles. See Section 7.1.1.2 for more details regarding step-dosing. All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[b] For subjects who discontinue investigational product, an end of treatment visit should occur as soon as possible (within 14 days) after the last dose of investigational product.

[c] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+ 3) days after the end of the last dose of investigational product or prior to initiation of other therapy, whichever occurs first.

[d] Assessed every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent. **During the long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen. As a study endpoint is overall survival, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following investigator's awareness of the event.**

[e] Each visit week and day is relative to day 1 of each cycle. Cycle 2 visits have a ± 1-day window from designated time point unless otherwise specified. All subsequent visits beginning in cycle 3 will have a ± 3-day window.













Table 2-4. Part 6: Schedule of Activities (Cycle 1 Only)

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]											Infusion-free interval	Notes
Week[c]		1				2			3	4			5	
Day[c]		1	2	3	4	8	9	10	15	22	23	24	29	
GENERAL / SAFETY ASSESSMENTS														
Informed consent	X													
Clinical evaluation	(X)	X	X	X	X	X	X	X	X	X	X	X	X	Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (see Section 9.2). Days 10 and 24 may performed by [redacted] or clinic visit per investigator discretion. (X): Additionally at screening: demographics, medical history, and height.
Vital signs, pulse ox	X	(X)		X	X	(X)		X	X	(X)		X	X	(X): Refer to Section 9.2.3.2 for detailed vital sign collection time points.
12-lead ECG (single)	X													
[redacted]														
ECHO or MUGA scan	X													
AE/DRE Review	(X)	Continually throughout study												(X): Only if related to study-mandated procedures
SAE Review		Continually throughout study												
Prior/concomitant medication		Continually throughout study												See Section 7.6; includes review of patient diary for protocol-required therapies administered at home [redacted]
LOCAL LABORATORY TESTING														
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	X	Laboratory assessments that were done within 24 hours prior to infusion do not need to be repeated. Blood samples must not be collected until at least 24 hours after PSMA or FDG PET scans.
Coagulation	X	X	X		X	X	X		X	X	X			
Chemistry panel	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X													

Abbreviations and footnotes defined on last page of table.

Table 2-4. Part 6: Schedule of Activities (Cycle 1 Only)

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]											Infusion-free interval	Notes
Week[c]		1				2			3	4			5	
Day[c]		1	2	3	4	8	9	10	15	22	23	24	29	
LOCAL LABORATORY TESTING (continued)														
Testosterone	X													
PSA		X												Additional unscheduled PSA measurements collected outside of this time point can be reported.
CENTRAL LABORATORY TESTS														
[redacted]														
PK sample collection		(X)												(X): See for Table 2-6 detailed AMG 160 and CYP PK collection schedule during treatment period.
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES														
Imaging	(X)													(X): See Table 2-7 – assessments are cycle independent
Premedication		X				X				X				Refer to Section 7.1.4 for details.
AMG 160 eIV infusion		X				X				X				
CYP cocktail	(X)													(X): Administered 24 hours prior to first dose of AMG 160.

Abbreviations and footnotes defined on last page of table.

Study Period/ Treatment Cycle	SCR[a]	Cycle 1[b]											Infusion-free interval	Notes
Week[c]		1				2			3	4			5	
Day[c]		1	2	3	4	8	9	10	15	22	23	24	29	
STUDY TREATMENT AND OTHER ASSESSMENTS/PROCEDURES (continued)														
Hospitalization/ monitoring	(X)	X				X				X				(X): Subjects are hospitalized 1 day prior to cycle 1 day 1. See Table 7-1 for additional guidance regarding hospitalization. Hospitalization beyond 72 hours may be allowed per investigator discretion.

AE = adverse event; ALP = alkaline phosphatase; C1D1 = cycle 1 day 1; CBC = complete blood count; DRE = disease-related event; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eIV = extended intravenous; **FDG = fluorodeoxyglucose;** HLA = human leukocyte antigen; IPIM = Investigational Product Instruction Manual; IV = intravenous; LDH = lactate dehydrogenase; MUGA scan = multigated acquisition scan; **PET = positron emission tomography;** PK = pharmacokinetic; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SCR = screening

[a] All screening procedures should be performed within 28 days prior to cycle 1 day 1 dosing.

[b] Please follow Table 2-5 for cycle 2 and subsequent cycles. All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion (EOI) assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[c] Each visit week and day is relative to day 1 of each cycle. Cycle 1 visits have a ± 1-day window from designated time point unless otherwise specified.

Table 2-5. Part 6: Schedule of Activities (Cycle 2 and Beyond)

Study Period/ Treatment Cycle	Cycle 2[a]							Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	
Week[e]	1			2	3		4	1	3				
Day[e]	1	2	3	8	15	16	22	1	15				Notes
GENERAL / SAFETY ASSESSMENTS													
Clinical evaluation	X	X	X	X	X	X	X	X	X	X	X		Includes physical exam, ECOG, and weight (neurological examination, if clinically indicated) (if indicated) (as described in Section 9.2).
Vital signs, pulse ox	(X)		X	X	(X)		X	X	X	X	X		(X): Refer to Section 9.2.3.2 for detailed vital sign collection time points
[redacted]													
AE/DRE review	Continually throughout study												
SAE review	Continually throughout study												
Prior/concomitant medication	Continually throughout study												See Section 7.6; includes review of patient diary for protocol-required therapies administered at home [redacted]
Survival status and/or subsequent cancer therapy												X	
LOCAL LABORATORY TESTS													
CBC with differential	X	X	X	X	X	X	X	X	X	X	X		Blood samples must not be collected until at least 24 hours after PSMA or FDG PET scans.
Coagulation	X	X		X	X	X	X	X	X	X	X		
Chemistry panel	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X							(X)					(X): Collected D1 of every other cycle (C2, C4, C6, etc.)
PSA	X							X		X	X		Additional unscheduled PSA measurements collected outside of these time points can be reported.

Page 1 of 2

Abbreviations and footnotes defined on last page of table.

Table 2-5. Part 6: Schedule of Activities (Cycle 2 and Beyond)

Study Period/ Treatment Cycle	Cycle 2[a]							Cycle 3+		EOT[b]	SFU[c]	LTFU[d]	
Week[e]	1			2	3		4	1	3				
Day[e]	1	2	3	8	15	16	22	1	15				Notes
CENTRAL LABORATORY TESTS													
[redacted]													
PK sample collection	(X)												(X): See for Table 2-6 detailed AMG 160 PK collection schedule during treatment period.
STUDY TREATMENT AND OTHER ASSESSMENTS / PROCEDURES													
Imaging	(X)												(X): See Table 2-7 – assessments are cycle independent
Premedication	X				X								Refer to Section 7.1.4 for details.
AMG 160 IV infusion	X				X			X	X				
CYP cocktail	X												Administered immediately after AMG 160 infusion.

[redacted]; AE = adverse event; ALP = alkaline phosphatase; C = cycle; CBC = complete blood count; D = day; DRE = disease-related event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; **FDG = fluorodeoxyglucose;** IPIM = Investigational Product Instruction Manual; IV = intravenous; LDH = lactate dehydrogenase; LTFU = long-term follow-up; PBMC = peripheral blood mononuclear cell; **PET = positron emission tomography;** PK = pharmacokinetic; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SCR = screening; SFU = safety follow-up

[a] Please follow Table 2-4 for the procedures/activities for cycle 1. See Section 7.1.1.2 for more details regarding step-dosing. All assessments on AMG 160 dosing days are performed pre-infusion. Assessments should not be performed from the infusion line. End of infusion assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM.

[b] For subjects who discontinue investigational product, an end of treatment visit should occur as soon as possible (within 14 days) after the last dose of investigational product.

[c] Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+ 3) days after the end of the last dose of investigational product or prior to initiation of other therapy, whichever occurs first.

[d] Assessed every 6 months up to 3 years from the first dose of protocol-required therapy for all subjects who have not withdrawn consent. **During the long-term follow-up phase serious adverse events suspected to be related to investigational product that the investigator becomes aware of will be reported to Amgen. As a study endpoint is overall survival, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following investigator's awareness of the event.**

[e] Each visit week and day is relative to day 1 of each cycle. Cycle 2 visits have a ± 1-day window from designated time point unless otherwise specified. All subsequent visits beginning in cycle 3 will have a ± 3-day window.

[redacted]

Table 2-6. Schedule of Pharmacokinetic Samples (All timepoints relative to AMG 160 dosing[e,f])





Table 2-7. Schedule of Imaging Assessments (Cycle Independent)

	SCR	Treatment Period[a]		EOT	SFU	LTFU	Notes
MRI brain	X						All subjects must have MRI of the brain performed within 28 days prior to the first dose of AMG 160. 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, bone scan[b], and tumor burden assessment	X	Weeks 1-24 Every 8 weeks	Weeks 25+ Every 12 weeks	X	X	X[c]	Radiologic imaging (CT/MRI) is required at the EOT or SFU visit if the subject has not had radiologic imaging performed within 6 weeks of the visit. Planar bone scintigraphy should be performed using conventional ^{99m}Tc-MDP radionuclide, or other equivalent ^{99m}Tc-labeled radiotracers.
^{68}Ga-PSMA-11 PET/CT[d]	X	Every 12 weeks		X			Blood samples [redacted] must not be collected until at least 24 hours after PSMA scan.
^{18}F-FDG PET/CT[d]	X						Dose-exploration phase Blood samples [redacted] must not be collected until at least 24 hours after FDG scan.
^{18}F-FDG PET/CT[d]	X	Every 12 weeks		X			Dose-expansion phase

^{99m}Tc-MDP = ^{99m}technetium methylene diphosphonate; CT = computed tomography; EOT = end of treatment; FDG = fluorodeoxyglucose; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; PET = positron emission tomography; PSMA = prostate specific membrane antigen; SCR = screening; SFU = safety follow-up

[a] Timing is based on first dose of AMG 160 (cycle 1 day 1) ± 7 days for imaging assessments.

[b] Per PCWG3 recommendations, the first post-treatment bone scan (at week 8) will be used as the baseline scan with which all future bone scans are compared.

[c] For subjects who discontinued treatment for any reason other than confirmed disease progression, every effort should be made to perform radiographic imaging (CT/MRI) of the chest, abdomen, pelvis, and all other known sites of disease every 3 months until documentation of confirmed disease progression per PCWG3 guidelines, clinical progression, biochemical progression, start of new anticancer therapy, or up to 3 years after the first dose of AMG 160, whichever occurs first.

[d] Both ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT scans are optional in [redacted], and Part 6.

Table 2-8. Summary of Step Dosing and Extended IV Infusion Schemas (Cycle 1)

	Cycle 1					Cycle 2+
	Day 1	Day 8	Day 15	Day 22	1-week infusion free	Dosing Days
3-day eIV (C1D1 only) + target dose						
AMG 160	1st step dose (3-day eIV)	Target dose (60-minute IV)	N/A	Target dose (60-minute IV)	Yes	D1 & D15
Part 2: [redacted]		X				D1
5-day eIV (C1D1 only) + target dose						
AMG 160	1st step dose (5-day eIV)	Target dose (60-minute IV)	N/A	Target dose (60-minute IV)	Yes	D1 & D15
Part 2: [redacted]		X				D1

C = cycle; D = day; eIV = extended intravenous; IV = intravenous; N/A = not applicable; [redacted]

3. Introduction

3.1 Study Rationale

Part 1: AMG 160 monotherapy

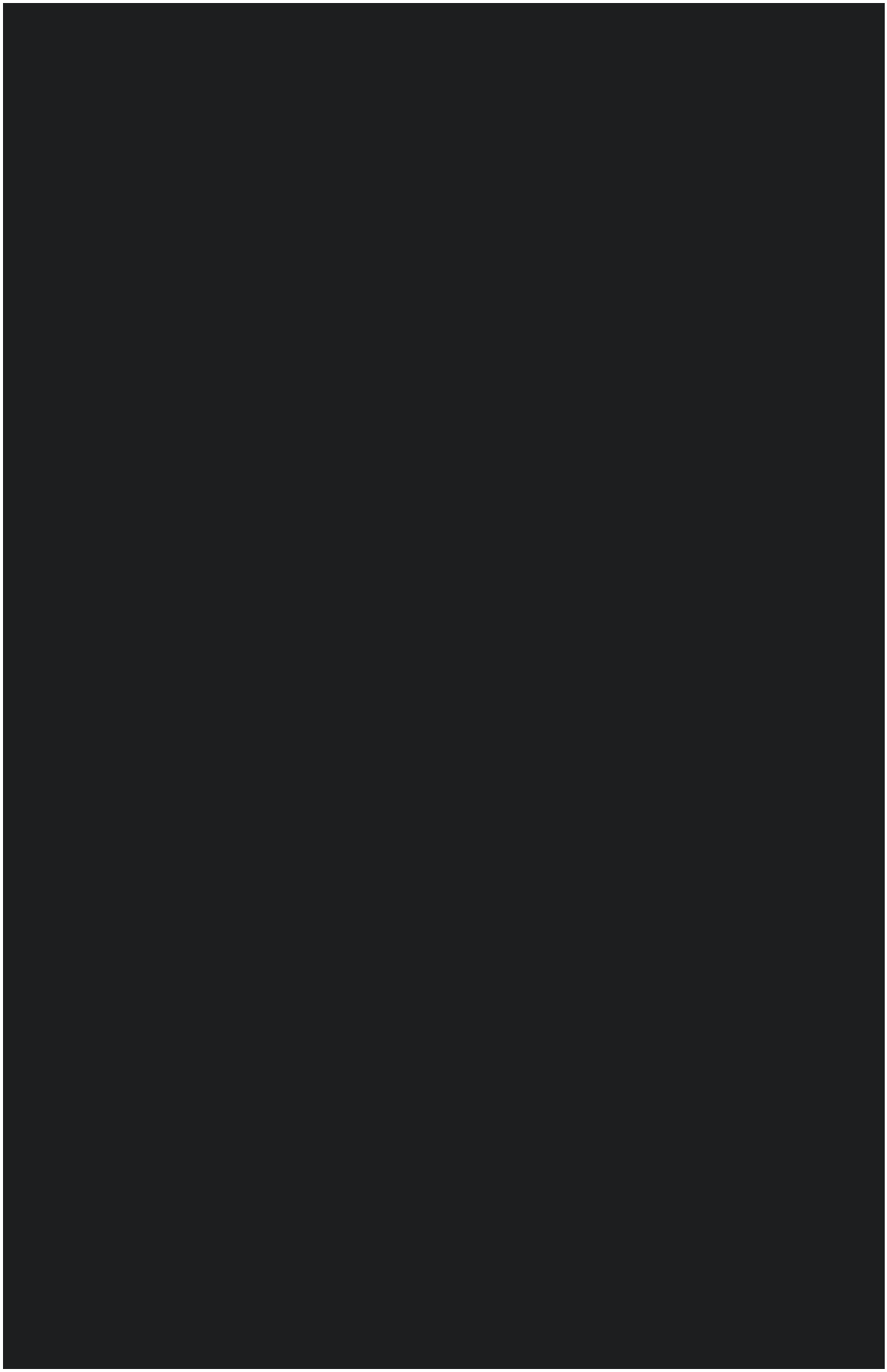
AMG 160 is a novel half-life extended (HLE) bispecific T-cell engager (BiTE®) molecule designed to direct T effector cells towards prostate-specific membrane antigen (PSMA)-expressing cells, with a single chain fragment crystallizable (scFc) moiety for extended half-life. Part 1 is a first-in-human study in adult subjects with metastatic castration-resistant prostate cancer (mCRPC) to assess AMG 160 safety and tolerability, pharmacokinetics (PK), and anti-tumor activity, with additional exploratory objectives to assess [redacted]

Part 2: AMG 160 Combination with Pembrolizumab

It has been shown that the BiTE molecule mode of action leads to an upregulation of immune checkpoints, such as PD-1 on immune cells and PD-L1 on tumor cells, and that the combination of the BiTE molecule blinatumomab with the PD-1 inhibitor nivolumab is safe and tolerable in subjects with acute lymphoblastic leukemia (ALL) with evidence of antitumor activity (Kobold, et al 2018; Webster, et al, 2018). Part 2 of the study will evaluate the safety and tolerability of AMG 160 given in combination with the PD-1 inhibitor pembrolizumab, with additional objectives to explore PK, pharmacodynamics, immunogenicity, and anti-tumor activity of AMG 160 when given in combination with pembrolizumab.

Part 3: Etanercept Prophylaxis for AMG 160-related CRS

Cytokine release syndrome (CRS) is an identified safety risk for AMG 160 and symptoms of CRS are partly mediated by the cytokine tumor necrosis factor alpha (TNF-α; Lee et al, 2014; Grupp et al, 2013). Recent preclinical and clinical studies involving cluster of differentiation (CD)3 bispecific immunotherapies with similar mechanisms of action as AMG 160 have reported that pretreatment with TNF-α inhibitors may mitigate CRS without affecting the antitumor activity (Li et al, 2019; Lee at al, 2014; Grupp et al, 2013; Lin et al, 2006). Part 3 will evaluate whether prophylaxis with the TNF-α inhibitor etanercept will decrease the frequency and severity of CRS without compromising the efficacy of AMG 160. If proven successful, etanercept and/or dexamethasone may be included in Parts 1 and[redacted]



[redacted]

Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

Elevated cytokines following AMG 160 administration may suppress CYP enzyme activity which may alter plasma concentrations of concomitant drugs that are metabolized via CYP mediated pathway. Therefore, Part 6 of this study will evaluate the effect of AMG 160 on plasma exposures of specific probes of CYP enzymes using a modified Cooperstown 5+1 CYP phenotyping cocktail.

3.2 Background

3.2.1 Disease

Prostate cancer is the second most frequent malignancy (after lung cancer) in men worldwide, counting 1 276 106 new cases and causing 358 989 deaths (3.8% of all deaths caused by cancer in men) in 2018 (Rawla 2019).

Metastasis is a primary cause of morbidity and mortality for prostate cancer. Since 1941, patients diagnosed with metastatic prostate cancer have received continuous androgen-deprivation therapy (ADT) in the form of surgical castration, chemical castration involving luteinizing hormone-releasing hormone agonist (LHRH)-modulating compounds, and/or antiandrogen therapy. In 2015, 2 trials (CHAARTED and STAMPEDE) demonstrated that in patients diagnosed with advanced prostate cancer, docetaxel combined with ADT conferred a 10 to 13.6 month improvement in median overall survival (OS) compared with ADT alone (James et al, 2016; Sweeney et al, 2015). In 2017, 2 trials (LATITUDE and STAMPEDE) demonstrated that the combination of ADT with abiraterone plus prednisone also conferred improvement in OS when compared to ADT alone (Fizazi et al, 2017; James et al, 2017). While abiraterone and docetaxel appear to have similar duration of survival benefit, the therapies differ significantly in their side effect profile, cost, and duration of treatment.

Metastatic prostate cancer often develops resistance to ADT due to increased intratumoral steroidogenesis, altered steroid-transporter expression, increased androgen receptor expression (eg, androgen receptor amplification), and other mechanisms

(Galletti et al, 2017). Since 2010, several therapies have been approved to treat these patients with mCRPC. Two novel hormonal therapies, enzalutamide and abiraterone, have demonstrated significant survival benefits in mCRPC patients. In first line mCRPC, abiraterone plus prednisone improved median OS from 30.3 to 34.7 months compared to placebo plus prednisone. Similarly, enzalutamide improved OS in the first line mCRPC setting (35.3 vs 31.3 months) (Sartor and de Bono, 2018). Radium-223 also demonstrated survival benefit (14.9 vs 11.3 months) in patients with bone metastases when combined with best standard care, which included older hormonal therapies, radiation, and bisphosphonates. Sipuleucel-T, an autologous cellular immunotherapy, increased median survival by 4.1 months compared with placebo, though prostate-specific antigen (PSA) and radiographic responses were not observed. Cabazitaxel, a tubulin-binding taxane, increased median survival by 2.4 months compared with mitoxantrone, though many trial participants did not complete treatment due to toxicity. Other therapies include bone-targeted agents such as zoledronic acid and denosumab, which reduced the rate of skeletal adverse events, including pathologic fractures and spinal cord compression (Litwin and Tan, 2017). Recently, pembrolizumab demonstrated limited activity (5% overall response rate [ORR]; n = 133) in patients with mCRPC and a number of combination trials with pembrolizumab are ongoing (Antonarakis et al, 2019).

While recently approved therapies have demonstrated survival benefits for patients with mCRPC, drug resistance often complicates the disease course and contributes to relapse and mortality. There is an urgent need for therapies with novel mechanisms of action to treat prostate cancers resistant to chemohormonal therapies. Recently, PSMA targeted therapies have shown activity in mCRPC patients (Hofman et al, 2018). PSMA is a 100 kDa type-II integral membrane glycoprotein that is mainly expressed on prostate epithelial cells (Christiansen et al, 2003; Israeli et al, 1993). PSMA is expressed in the prostate and in a limited number of tissues, including in a subset of renal proximal tubules, some cells of the intestinal brush-border membrane, liver and rare cells in the colonic crypts (O'Keefe et al, 2004; Chang et al, 1999b; Troyer et al, 1995; Israeli et al, 1994; Lopes et al, 1990; Horoszewicz et al, 1987). In prostate cancer, expression of PSMA increases with disease progression and is highest in metastatic disease, hormone refractory cases, and higher-grade lesions. There is a strong correlation between a negative prognosis and cell surface expression of PSMA. Consistent with the correlation between PSMA expression and tumor stage, increased levels of PSMA are associated with androgen-independent prostate cancer

(Wright et al, 1996; Israeli et al, 1994). Immunohistochemical analysis revealed relatively intense and homogeneous expression of PSMA within metastatic lesions localized to lymph nodes, bone, soft tissue, and lungs compared with benign prostatic tissues (Chang et al, 2001a; Sweat et al, 1998; Murphy et al, 1996). The restricted expression of PSMA and its up-regulation in advanced carcinoma and metastatic disease has spurred the development of PSMA-targeted therapies for prostate cancer, including radiopharmaceutical therapies and immunotherapies.

3.2.2 Amgen Investigational Product Background

3.2.2.1 AMG 160

BiTE® molecules are designed to direct T effector cells towards target cells. The proximity induced by the BiTE® molecule triggers target cell specific cytotoxicity which closely resembles standard cytotoxic T lymphocyte activation. Blinatumomab (BLINCYTO®), a CD19 BITE® molecule, is approved for the treatment of acute lymphoblastic leukemia (ALL).

AMG 160 is an HLE BiTE® molecule designed to direct T effector cells (via CD3 binding) to prostate cancer cells expressing PSMA. In addition to binding domains specific for CD3 and PSMA, AMG 160 contains the N-terminus of an immunoglobulin (Ig)G scFc region. The fusion to the fragment crystallizable (Fc) domain is a well-established strategy to prolong the half-life of protein therapeutics, such as cytokines, growth factors, and bispecific antibodies, with several approved for the treatment of cancer (Kontermann, 2011). The extended half-life of Fc fusion proteins is due to their interaction with the neonatal Fc receptor, which results in a protected intracellular protein reservoir that is recycled to the extracellular space (Rath et al, 2015).

A detailed description of the chemistry and pharmacology of AMG 160 is provided in the AMG 160 Investigator's Brochure.

3.2.2.1.1 Nonclinical Pharmacology

The activity of AMG 160 requires the simultaneous binding to both target cells and T cells. The pharmacological effect of AMG 160 is mediated by specific redirection of previously primed cytotoxic $CD8^+$ or $CD4^+$ T lymphocytes to kill PSMA-expressing cells.

As part of the T cell activation process, BiTE® molecules, such as AMG 160, cause the formation of a cytolytic synapse between T cells and target cells. The subsequent release of the pore-forming protein perforin and the apoptosis-inducing proteolytic enzyme granzyme B by T cells results in the induction of apoptosis in the target cells.

AMG 160-mediated T cell activation not only induces the directed release of cytotoxic proteins to target cells, but also results in a transient production of inflammatory cytokines such as interferon gamma (IFN-γ), TNF, interleukin-2 (IL-2) and IL-6 by T cells.

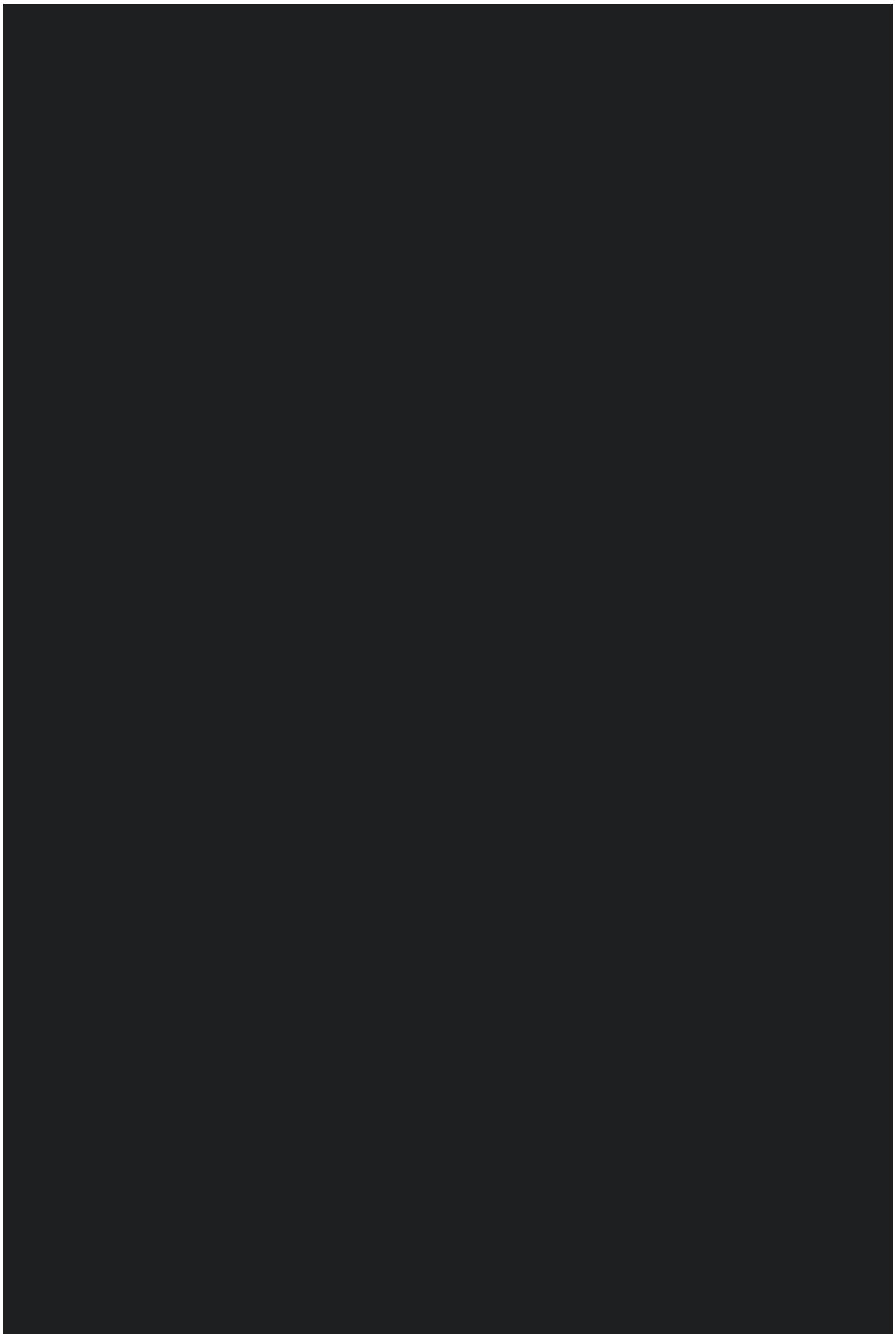
AMG 160 monotherapy significantly inhibited growth of established subcutaneous 22Rv1 and prevented the development of subcutaneous 22Rv1 tumors in a tumor formation study.

3.2.2.1.2 Nonclinical Pharmacokinetics

[redacted]

3.2.2.1.3 Nonclinical Toxicology

[redacted]





3.2.2.1.4 Clinical Experience

Study 20180101 evaluated various dosing schedules involving step-dosing and eIV infusion in cycle 1. Doses ranged from 0.003 to 0.9 mg. Initially, 36 subjects were enrolled in the Part 1 step-dosing cohorts (data cutoff date 19 January 2021). Subsequently 58 subjects were enrolled into Part 1 eIV dose escalation and dose expansion cohorts (data cutoff 09 March 2021) which showed an improved benefit/risk profile relative to step-dosing cohorts. As of 11 May 2021, 17 subjects had been enrolled in Part 2 (AMG 160 + pembrolizumab).

For the Part 1 step-dosing cohorts, 3 subjects (8.3%) remained on treatment, and 33 subjects (91.7%) discontinued investigational product (due to disease progression [77.8%], subject request [8.3%], adverse event [2.8%], and requirement for alternative therapy [2.8%]). Seven subjects (19.4%) remained on treatment for more than 6 months. For the Part 1 eIV cohorts, 33 subjects (56.9%) remained on treatment, and 22 subjects (37.9%) discontinued investigational product (due to disease progression [20.7%], subject request [10.3%], adverse event [5.2%], and requirement for alternative therapy [1.7%]). Seven subjects (12.1%) remained on treatment for more than 6 months.

In Part 2, [redacted] subjects [redacted]%) remained on treatment and [redacted] subjects [redacted]%) discontinued investigational product. Adverse events considered by the site investigator to be related to investigational product were reported for [redacted] subjects ([redacted]%). No DLTs were observed within dose cohorts 3 and 4 (eIV).

A number of mitigations were implemented on study to improve the safety profile, including step dosing (lower dose prior to target dose), 3-day eIV infusion for the first dose in cycle 1, corticosteroid premedication (IV, oral [PO], and [redacted]), and prophylactic IV hydration. These measures improved the safety profile, reducing the incidence and severity of CRS events. The MTD/RP2D of the study was declared as [redacted] mg 3-day eIV infusion in week 1 followed by [redacted] mg target dose in week 2 (and every 2 weeks thereafter) along with prophylactic mitigations, including dexamethasone premedication in cycle 1, prophylactic [redacted] in cycles 1 to 2, and optional prophylactic IV hydration in cycle 1.

3.2.2.1.4.1 Clinical Safety

The key treatment-related safety risk was CRS associated with fever, vomiting, diarrhea, transaminitis, and/or hypotension (grading by Lee et al, 2014 criteria). CRS events occurred predominantly in cycles 1 and 2 and were reversible and manageable with standard mitigation approaches (eg, tocilizumab, corticosteroids, vasopressors). Transaminitis events were short-term (1 to 3 days) and reversible AST/ALT elevations not associated with long-term hepatic dysfunction and occurred predominantly in cycle 1 (first dose effect).

In Part 1, 94.4% of subjects in the step-dosing cohort and 96.4% of subjects in the eIV cohorts had treatment-related CRS. The majority of events were grade 2 (80.6% of subjects in step-dosing cohort; 70.9% of subjects in eIV cohorts). Additionally, grade 3 events (36.1% of subjects in step-dosing cohort; 18.2% of subjects in eIV cohorts) and 1 grade 4 event (1.8% of subjects in eIV cohorts) have been reported.

CRS was the most commonly reported adverse event in both cohorts. In addition to CRS, the most commonly reported adverse events in the step-dosing cohort were fatigue, constipation, nausea, vomiting, headache, and pyrexia. In the eIV cohorts, the most commonly reported adverse events were diarrhea, fatigue, dry mouth, nausea, and dysgeusia.

[redacted]

In Part 2, cohort 1 (n = [redacted] subjects, [redacted] subjects not DLT evaluable), AMG 160 [redacted] mg target dose given as 1-step dose) in combination with pembrolizumab was well tolerated

with no DLTs. [redacted] subjects had reversible, treatment-related grade 3 events considered to be serious (atrial fibrillation and diarrhea). There were [redacted] grade 2 CRS events and no grade 3, 4, or 5 CRS events. In cohort 2 (n = [redacted] subjects), AMG 160 [redacted] mg target dose given as 2 step-dose) in combination with pembrolizumab was not tolerated with [redacted] reversible grade 4 uveitis leading to treatment discontinuation. There were [redacted] grade 2 CRS events and no grade 3, 4, or 5 CRS events. [redacted] subject experienced grade 2 anterior uveitis leading to pembrolizumab discontinuation. In cohort 3 (n = [redacted], AMG 160 [redacted] mg target dose given with initial [redacted] mg 3-day eIV in week 1 in combination with pembrolizumab [redacted] was well tolerated with no ocular events and no grade 3, 4, or 5 CRS events. Cohort 4 [redacted] mg target dose with initial [redacted] mg 3-day eIV in week 1 in combination with pembrolizumab [redacted] is currently open with [redacted] subjects enrolled; analysis of safety and efficacy are ongoing.

As of 02 March 2021, preliminary PK data for AMG 160 were available for [redacted] subjects. Within the evaluated dose range, among subjects who were tested negative for [redacted] the serum AMG 160 exposures increased in an approximately dose proportional manner with an estimated mean terminal elimination half-life of approximately 3 to 5 days.

As of 20 May 2021, in Part 1 (AMG 160 monotherapy), across all evaluated target dose levels, treatment-emergent [redacted] have been detected in 32/90 subjects (35.6%) who have had at least 1 post baseline assessment available beyond cycle 2 day 1 (or until end of treatment, whichever occurred first). Of these 32 subjects, 23 experienced loss in exposure (ranging from 50% to 100% loss). In Part 2 (AMG 160 + pembrolizumab), [redacted] were detected in [redacted] subjects ([redacted]%). Of these [redacted] subjects, [redacted] experienced loss in exposure. No adverse events clearly associated with [redacted] were observed.

3.2.2.1.4.2 Clinical Efficacy

In the Part 1 step-dosing cohorts (data cutoff 19 January 2021, n = 36), Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 with Prostate Cancer Working Group 3 (PCWG3) responses among the 20 evaluable subjects (subjects who received at least 1 dose of AMG 160 and had measurable baseline disease) included 2 subjects with an objective response. Of the 36 subjects (100%) who had baseline PSA measurements, 11 subjects (30.6%) had confirmed PSA reductions of ≥ 30%, 6 subjects (16.7%) had PSA reductions of ≥ 50%, 3 subjects (8.3%) had PSA reductions of ≥ 70%, and

2 subjects (5.6%) had PSA reductions of ≥ 90% (confirmed responses only). Two subjects (8.3%) achieved CTC0 responses at week 13. The median duration of exposure to AMG 160 was 17.2 weeks.

In the Part 1 eIV cohorts (data cutoff 09 March 2021, n = 58), RECIST 1.1 with PCWG3 modification responses among the 22 evaluable subjects included 2 subjects (9.1%) with an objective response. Of the 55 subjects who had baseline PSA measurements (94.8%), 21 subjects (38.2%) had confirmed PSA reductions of ≥ 30%, 17 subjects (30.9%) had PSA reductions of ≥ 50%, 14 subjects (25.5%) had PSA reductions of ≥ 70%, and 7 subjects (12.7%) had PSA reductions of ≥ 90%. No subject achieved CTC0 response at week 13. The median duration of exposure to AMG 160 was 9.0 weeks.

Best overall response (RECIST 1.1 with PCWG3 modification) for all evaluable subjects in the Part 1 step-dosing and eIV cohorts (data cutoff 19 January 2021; n = 25) included 4 subjects with confirmed partial response, 1 subject with unconfirmed partial response, 12 subjects with stable disease, 6 subjects with progressive disease, and 2 subjects who were not evaluable. As of the data cutoff, the majority of subjects in the eIV cohort had not had on-treatment response assessments.

For Part 2, RECIST 1.1 evaluation among the [redacted] subjects with measurable disease included [redacted] subjects with stable disease. Three of [redacted] evaluable subjects [redacted]%) achieved PSA reductions [redacted]% and [redacted] subject had a CTC0 response. In cohort 3, [redacted] subjects were evaluable with [redacted] PSA reductions [redacted]% and [redacted] PSA reduction [redacted]%, as well as [redacted] subjects with stable disease. In cohort 4, [redacted] subjects were evaluable with 1 PSA reduction [redacted]%. This cohort is currently open and enrolling. Data continues to be assessed for safety and efficacy.

3.2.2.2 Part 3 only: Etanercept

Recent preclinical and clinical studies involving CD3 bispecific immunotherapies with similar mechanisms of action as AMG 160 have reported that pretreatment with TNF-α inhibitors may mitigate CRS without affecting antitumor activity (Li et al, 2019; Lee et al, 2014; Grupp et al, 2013; Lin et al, 2006).

In this study, etanercept (investigational use of a marketed product) will be used prophylactically to mitigate signs, symptoms, and severity of CRS. Etanercept is not approved for the disease/condition being studied. Etanercept is a protein containing the extracellular domains of 2 p75 human TNF receptors attached to the Fc portion of a

type 1 human immunoglobulin (IgG1) (Mohler et al, 1993). Because etanercept acts primarily by binding and neutralizing both soluble and cell-bound TNF, it has potential applications in many clinical settings in which TNF plays a major pathogenic role.

Refer to the regional prescribing information for etanercept for additional information.

3.2.3 Non-Amgen Investigational Product Background

3.2.3.1 Pembrolizumab (Part 2 Only)

Pembrolizumab is a humanized IgG4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Keytruda® (pembrolizumab) is indicated for the treatment of subjects across a number of indications and is in clinical development for a number of other malignancies, including prostate cancer.

Refer to the regional prescribing information for Keytruda (KEYTRUDA United States Prescribing Information, 20**22**) for additional information.

3.3 Benefit/Risk Assessment

Part 1: AMG 160 Monotherapy

Part 1 is the first-in-human study of AMG 160 monotherapy in adult subjects with mCRPC. Based on nonclinical toxicity studies of AMG 160, and clinical experience with other BiTE® molecules and PSMA targeting agents, the anticipated benefit/risk profile favors clinical development of AMG 160 for subjects with mCRPC. The following benefit risk assessment supports the conduct of this clinical trial. Please refer to the Investigator's Brochure for further data on AMG 160.

Part 2: AMG 160 Combination With Pembrolizumab

Part 2 is the first-in-human study of AMG 160 in combination with pembrolizumab in adult subjects with mCRPC. The following benefit risk assessment supports the conduct of this clinical trial. Refer to the regional prescribing information for Keytruda (KEYTRUDA United States Prescribing Information, 20**22**) for additional safety information.

Part 3: Etanercept Prophylaxis for AMG 160-related CRS

In Part 1 of this study, CRS was established as an identified risk of AMG 160. In order to mitigate this risk of CRS, Part 3 will investigate the use of etanercept in combination

or alone with dexamethasone prior to AMG 160 in cycle 1 only. The benefit risk assessment of etanercept supports the conduct of Part 3.



Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

Anticipated risk/benefit is the same as Part 1.

3.3.1 Therapeutic Context

PSMA targeted therapies have recently shown promise in mCRPC. In a phase 2 study involving mCRPC patients refractory to standard of care therapies, ^{177}Lu-PSMA-617 demonstrated significant rates of objective response (OR) and PSA response as well as improvements in quality of life assessments (Hofman et al, 2018). Key outstanding issues for PSMA radiopharmaceuticals involve grade 3 to 4 bone marrow toxicities driven by the radioactive moiety as well as primary resistance to therapy and lack of response durability. While PSMA has been established as a therapeutic target for mCRPC, there is a need for new PSMA targeted therapies with novel modalities that permit improved safety, patient access, and durability of responses.

Cancer immunotherapies have demonstrated durable clinical responses and certain classes of immunotherapies are active in mCRPC. The first Food and Drug Administration (FDA)-approved immunotherapy for prostate cancer, Sipuleucel-T, is a personalized cancer vaccine targeting prostatic acid phosphatase (PAP) that conferred an OS benefit for mCRPC patients (withdrawn from EU). Recently, the immune

checkpoint inhibitor pembrolizumab demonstrated activity in mCRPC patients with microsatellite instability (MSI), comprising 5% of the patient population (Comiskey et al, 2018). There is a need for novel immunotherapies that are active in the broader mCRPC population.

BiTE® molecules exert a common mechanism of action involving engagement of T cells and target cells leading to redirected lysis of the target cells. Therefore, experiences with other BiTE® molecules provide a therapeutic context for AMG 160.

The most advanced BiTE® molecule is blinatumomab, which is FDA approved for the treatment of B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% and relapsed or refractory B cell precursor ALL. Blinatumomab targets CD3 and CD19 and is administered by continuous IV infusion. Clinical trials in late-stage hematological malignancies demonstrated an acceptable safety profile with clinical responses, leading to breakthrough designation and accelerated approval by the FDA (BLINCYTO United States Prescribing Information, 2018). In the EU, conditional license for blinatumomab was granted in 2015 and full license approved in 2018. The most common adverse reactions ($\geq$ 20%) are infections, pyrexia, headache, infusion-related reactions, anemia, febrile neutropenia, thrombocytopenia, and neutropenia. According to the US prescribing information (BLINCYTO United States Prescribing Information, 2018), additional adverse reactions included CRS, neurological toxicities, infections, tumor lysis syndrome (TLS), neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, pancreatitis, leukoencephalopathy, and preparation/administration errors. The combination of blinatumomab with the PD-1 inhibitor nivolumab was reported to be safe and tolerable in a phase 1 study of subjects with acute lymphoblastic leukemia (ALL) with evidence of antitumor activity (Webster, et al, 2018).

Several other BiTE® molecules have entered clinical trials. Adverse events common to these constructs and blinatumomab include fatigue and CRS (particularly fever).

3.3.2 Key Benefits

This is the first-in-human trial of AMG 160. Key benefits in humans will be investigated and will be described when the data become available. Potential benefits include reduction or regression of prostate cancer disease burden.

3.3.3 Key Risks

3.3.3.1 AMG 160

Based on biological mechanism, nonclinical toxicity studies of AMG 160, and**/or** clinical experience, [redacted]

[redacted]

Table 3-1. Key Safety Risks for AMG 160

[redacted]

[redacted]

Clinical signs and symptoms of [redacted] will be **continuously** monitored **throughout the duration of** the study and at the time points **indicated in the Schedule of Activities (Section 2.2)**. Refer to Table 7-9, Section 7.1.4, and Section 12.14 for specific recommendations regarding the mitigation and management of these risks.

Coronavirus disease 2019 (COVID-19) infection may theoretically increase the signs and symptoms of CRS. Subjects with acute symptoms of COVID-19 disease within 10 days prior to first dose of AMG 160 (counted from day of positive test for asymptomatic subjects) are excluded from study. See Section 12.17 for additional guidance related to COVID-19.

Please refer to the AMG 160 Investigator's Brochure for further description of the key safety risks.

3.3.3.2 Pembrolizumab (Part 2 only)

Among the many immunotherapeutic strategies, immune checkpoint blockade enhances a cancer patient's immune system to fight an array of cancers. By increasing the activity of the immune system, immune checkpoint blockade can induce inflammatory side effects known as immune-related Adverse Events (irAE). Although any organ system can be affected, immune-related adverse events most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver. Less often, the central nervous system and cardiovascular, pulmonary, musculoskeletal, and hematologic systems are involved. The wide range of potential immune-related adverse events requires multidisciplinary, collaborative management by providers across the clinical spectrum.

Immune-related adverse reactions may be mild to moderate in severity but can be severe or fatal and can occur in any organ system or tissue in patients receiving

pembrolizumab and may also occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, there should be adequate evaluation to confirm etiology and exclude other causes.

The key safety risks for pembrolizumab include immune-related toxicities, infusion-related reactions, and embryofetal toxicity (Table 3-2).

Table 3-2. Key Risks for Pembrolizumab

Safety Risk	Description
Immune-related toxicities	Immune-related adverse effects associated with PD-1 blocking agents include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin reactions, encephalitis, vasculitis, sclerosing cholangitis, and other immune-related adverse reactions.
Infusion-related reactions	Signs and symptoms may include pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain.
Embryofetal toxicity	Blockade of PD-1 signaling has been shown in animal models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, there is the possibility of fetal harm if administered during pregnancy.

Refer to the regional prescribing information for Keytruda (KEYTRUDA United States Prescribing Information, 20**22**) for additional safety information.

AMG 160 Combination With Pembrolizumab

In a phase 1 study, the combination of the BiTE molecule blinatumomab with the PD-1 inhibitor nivolumab was reported to be safe and tolerable in a small number of subjects with acute lymphoblastic leukemia (ALL) (Webster et al, 2018). Refer to Section 3.2.2.1.4.1 for clinical safety information that is available for the combination of AMG 160 with pembrolizumab. Based on biological mechanism of action and initial clinical safety information from the monotherapy study with AMG 160, and from the subjects enrolled to the AMG 160 plus pembrolizumab arm the key safety risks described for monotherapy would also be expected along with the potential risks described for pembrolizumab. Moreover, with combination treatment, adverse events may be more severe and occur at different time points and/or dose levels in comparison to monotherapy. In particular, target-dependent and target-independent synergistic activation of T cells is expected and may contribute to more severe immune-related toxicities.

Clinical signs and symptoms of immune-related toxicities, CRS and infusion-related reactions, along with safety laboratory parameters, will be closely monitored during the study. Refer to Table 7-9 for specific recommendations regarding the mitigation and management of CRS and infusion-related reactions.



In light of potential overlapping toxicities with AMG 160 and pembrolizumab, additional eligibility criteria have been introduced. Patients will be hospitalized after administration of AMG 160 and pembrolizumab to monitor for these potential safety risks (refer to Table 7-1). Refer to (NCCN Clinical Practice Guideline, 2019) for specific recommendations regarding the mitigation and management of immune-related toxicities.

3.3.3.3 Etanercept (Part 3 only)

As of 02 February 2019, approximately 14 595 people have received etanercept in Amgen-sponsored research studies. Since it was first approved for sale through 02 February 2019, worldwide exposure to etanercept is estimated to be 6 628 257 patient-years.

The key safety risks for etanercept include injection site reactions, infections, allergic reactions, and development of autoantibodies (Table 3-3). Refer to the regional prescribing information for additional safety information.

Table 3-3. Key Risks for Etanercept

Safety Risk	Description
Injection site reactions	Symptoms include redness, tenderness, pain, bruising, warmth, swelling, itching, and/or infection at the injection site.
Infections	It is possible that etanercept may make infections worse and that an infection could result in serious illness. Both non-serious and serious infections have been reported in both adults and children in clinical studies, and include viral, bacterial (including tuberculosis), and fungal infections. Infections have been noted in all areas of the body.
Allergic reactions	These reactions may include headache, flushing, shortness of breath, itching and rash on any part of the body. Hives (itchy raised red bumps on the skin) may develop or more severe and serious allergic reactions such as dizziness, difficulty breathing, a decrease in blood pressure and/or swelling of parts of the body, the mouth, tongue, and/or throat also occur rarely. Swelling can occur over a period of minutes to several hours after administration of etanercept.
Development of autoantibodies	Signs and symptoms may include arthritis-type joint pain, fatigue, fever, rashes, cold or allergy-type symptoms, weight loss, and muscular weakness. Rare cases of a lupus-like syndrome have been reported.
Fever	
Headache (very common)	
Other potential risks (uncommon)	Non-melanoma skin cancer, psoriasis, uveitis, scleritis, neutropenia, thrombocytopenia, anemia, congestive heart failure, systemic and cutaneous vasculitis, elevated liver enzymes.

AMG 160 Combination with Etanercept (Part 3 only)

Clinical safety information is currently emerging for the combination of AMG 160 with etanercept. Based on biological mechanism of action and initial clinical safety information from the monotherapy study with AMG 160, some of safety risks described for monotherapy would also be expected along with the potential risks described for etanercept. Moreover, with combination treatment, adverse events may be more severe in comparison to monotherapy. In particular, development or worsening of infections while taking immunosuppressive medications such as dexamethasone pre-medication, development or worsening of CRS-associated fever, development or worsening of uveitis, development or worsening of thrombocytopenia, development or worsening of CRS associated liver enzyme elevation cardiac arrhythmias could exacerbate the AMG 160 associated potential risk of [redacted].

[redacted]

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Parts 1, 3 [redacted] and 6: AMG 160 monotherapy	
Objectives	**Endpoints**
Primary	
• Evaluate the safety and tolerability of AMG 160 in adult subjects • **Part 1 only:** Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D)	• dose-limiting toxicities (DLTs) • treatment-emergent adverse events • treatment-related adverse events • changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 160	• PK parameters for AMG 160 following intravenous (IV) administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate preliminary anti-tumor activity of AMG 160	• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%) • duration of response (DOR) (per RECIST 1.1) • PSA DOR based on PSA50 response • ^{68}Gallium (^{68}Ga)-prostate-specific membrane antigen (PSMA)-11 positron emission tomography(PET)/computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) PET/CT based response evaluation (Parts [redacted] and 6 are not included) • time to progression (radiographic and PSA) • progression-free survival (PFS) (radiographic and PSA) • 1, 2, and 3-year overall survival (OS) • circulating tumor cells (CTCs) – response (CTC0) and rate of CTC conversion

	• other Prostate Cancer Working Group 3 (PCWG3)-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase [LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)
• Part 6 only: Evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma exposures of specific probes of CYP enzymes	• PK parameters of specific probes of CYP enzymes including, but not limited to, C_{max}, area under the concentration-time curve over a 24-hour period (AUC24) and, if feasible, $t_{1/2}$
Part 2: AMG 160 in combination with pembrolizumab	
Objectives	**Endpoints**
Primary	
• Evaluate the safety and tolerability of AMG 160 in combination with pembrolizumab in adult subjects • Determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of AMG 160 in combination with pembrolizumab	• dose-limiting toxicities (DLTs) • treatment-emergent adverse events • treatment-related adverse events • changes in vital signs, electrocardiogram (ECG), and clinical laboratory tests
Secondary	
• Characterize the pharmacokinetics (PK) of AMG 160 in combination with pembrolizumab	• PK parameters for AMG 160 following intravenous (IV) administration including but not limited to maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), area under the concentration-time curve (AUC) over the dosing interval, accumulation following multiple dosing, and, if feasible, half-life ($t_{1/2}$)
• Evaluate preliminary anti-tumor activity of AMG 160 in combination with pembrolizumab	• objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 • prostate-specific antigen (PSA) response (30%, 50%, 70%, 90%) • duration of response (DOR) (per RECIST 1.1) • PSA DOR based on PSA50 response • ^{68}Ga-PSMA-11 PET/ CT and ^{18}F-FDG PET/CT based response evaluation • time to progression (radiographic and PSA) • progression-free survival (PFS) (radiographic and PSA) • 1, 2, and 3-year overall survival (OS) • circulating tumor cells (CTCs) – response (CTC0) and CTC conversion • other PCWG3-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], lactate dehydrogenase

	[LDH], hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide)

Parts 1, 3, [redacted]	
Objectives	**Endpoints**
Exploratory	
[redacted]	

Part 2: AMG 160 in combination with pembrolizumab	
Objectives	**Endpoints**
Exploratory	
[redacted]	

[redacted]

4.2 Hypothesis

AMG 160 monotherapy and in combination with pembrolizumab will demonstrate acceptable safety and tolerability in subjects with mCRPC at 1 or more dose levels with at least 1 dose level showing preliminary evidence of anti-tumor activity. No formal hypotheses will be tested.

5. Study Design

5.1 Overall Design

5.1.1 Part 1: AMG 160 Monotherapy

Part 1 is an open-label, ascending, multiple dose, phase 1 study evaluating AMG 160 administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC (up to 190 subjects). To reduce the incidence of CRS, the cycle 1 dosing schedule may be adapted to include an alternate dosing schedule involving a planned 3-day eIV infusion (with the option to modify to range from 2-day to 7-day infusion) within the first week of cycle 1 followed by target doses (short-term IV infusions).

The study will consist of:

- dose-exploration phase (Section 7.4.1.1)
- dose-expansion phase (1a and 1b) (Section 7.4.1.2)

The dose-exploration phase of the study will estimate the MTD of AMG 160 using a Bayesian logistic regression model (BLRM; Neuenschwander et al, 2008). Recommended phase 2 dose may be identified based on emerging safety, efficacy, and pharmacodynamic data prior to reaching an MTD. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.

Following the dose-exploration phase in Part 1, a dose-expansion phase will be conducted in 2 parts (1a and 1b) to confirm safety, PK, and pharmacodynamics at the MTD or RP2D and to obtain further safety and efficacy data [redacted] analysis. Dose expansion 1a will enroll approximately 50 subjects, independent of

PSMA status. Dose expansion 1b will enroll approximately 50 subjects [redacted]

During the dose exploration phase, individual cohorts of subjects from [redacted] will be enrolled with a safety lead-in at 1 or more dose levels below the MTD or RP2D followed by evaluation at the MTD or RP2D to confirm the safety, tolerability, MTD and/or RP2D of AMG 160 in [redacted] subjects, respectively.

Additional subjects may be enrolled in 1 or more monotherapy dose levels that have been shown to be safe and tolerable (defined as backfill enrollment). This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and pharmacodynamics for AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

5.1.2 Part 2: AMG 160 Combination with Pembrolizumab

This combination dose exploration study (n = **3**0) will explore the safety, **PK**, and efficacy of AMG 160 in combination with the PD-1 inhibitor pembrolizumab in approximately **3**0 subjects with mCRPC.

AMG 160 will be administered as a short-term IV infusion (approximately 60 minutes) every 2 weeks in a 28-day cycle in subjects with mCRPC. The starting dose of AMG 160 will be 1 dose level below the dose level that has been recommended as safe and tolerable by DLRT. To reduce the incidence of CRS, the cycle 1 dosing schedule includes a multi-step dosing schedule (see Section 7.1.1.2). Pembrolizumab will be dosed [redacted] on AMG 160 dosing days beginning with the first AMG 160 target dose, and pembrolizumab infusion will take place after AMG 160 infusion and post-infusion flush. The DLRT may modify the AMG 160 and pembrolizumab dosing schedule based on emerging safety data.

This dose exploration study will estimate the MTD and/or RP2D of AMG 160 in combination with pembrolizumab using a modified toxicity probability interval design (mTPI-2; Section 12.16). Recommended phase 2 dose may be identified based on emerging safety, efficacy, pharmacokinetic, and pharmacodynamic data prior to reaching an MTD. If necessary, 10 additional subjects may be enrolled at the RP2D for subjects in order to obtain additional safety and pharmacokinetic data. Alternative dosing schedule(s) may be explored based on emerging PK and safety data.

5.1.3 Part 3: Etanercept Prophylaxis for AMG 160-related CRS

Part 3 will evaluate the effect of etanercept premedication on the safety, tolerability, and efficacy of AMG 160. Specifically, Part 3 will assess whether prophylaxis with the TNF-α inhibitor etanercept might decrease the frequency and severity of CRS without compromising the efficacy of AMG 160.

[redacted]

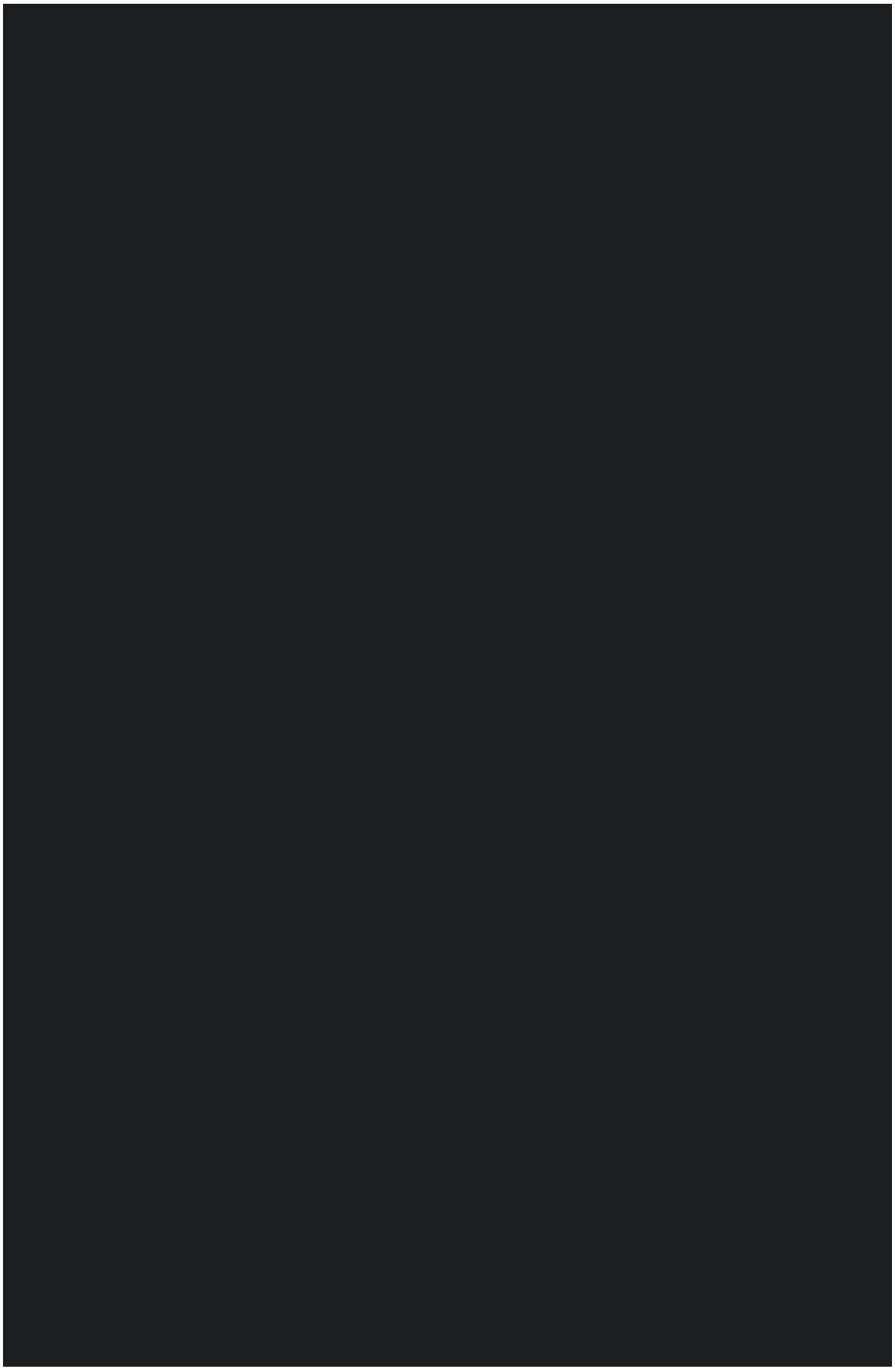
Subject incidence of safety events, including dose-limiting toxicities (DLTs), serious adverse events, and adverse events leading to treatment discontinuation or dose reduction, will be reviewed when at least 3 DLT-evaluable subjects complete the DLT window. If etanercept does not reduce the signs and symptoms of CRS, enrollment in Part 3 will be discontinued.

If etanercept prophylaxis reduces signs and symptoms of CRS and improves tolerability of AMG 160 in cohort 1, an additional cohort of 6 to 8 subjects may receive AMG 160 with etanercept prophylaxis only (ie, without dexamethasone premedication) [redacted] prior to each cycle 1 dose of AMG 160. Based on safety data, additional subjects (up to 20 in the cohort) may be enrolled in Part 3 to evaluate the effect of etanercept premedication (with or without dexamethasone premedication) on the safety, tolerability, and efficacy of AMG 160. Refer to Figure 2-3.

If etanercept reduces signs and symptoms of CRS without impacting efficacy in Part 3, etanercept prophylaxis (with or without dexamethasone prophylaxis) may be added to Parts 1, 2, [redacted]

Part 3 will be conducted in US and Canada only.

[redacted]





5.1.6 Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort

Part 6 of this study will evaluate the effect of co-administration of multiple dosing of AMG 160 on plasma exposures of specific probes of CYP enzymes using a modified Cooperstown 5+1 CYP phenotyping cocktail. Up to 8 subjects are planned to be enrolled. Briefly, each subject will receive a single oral dose of all components of the CYP phenotyping cocktail one day prior to cycle 1 day 1 and subsequently on cycle 2 day 1. AMG 160 will be administered at the MTD/RP2D as determined in Part 1.

Part 6 will be conducted in **the** US and Singapore.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 218 to 288 subjects will be enrolled in US, Canada, Asia, Europe, and Australia in this study.

	Number of Subjects		
Study Part	Total	Subsets	
Part 1: AMG 160 monotherapy	120-190	Dose exploration	70-90
		Step-dosing	30
		eIV	20
		[redacted]	
		Backfill (optional)	20
		Dose expansion	100
		Expansion 1a	50
		Expansion 1b	50
Part 2: AMG 160 in combination with pembrolizumab	30		
Part 3: Etanercept prophylaxis for AMG 160-related CRS	20		
[redacted]			
Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort	8		
Total	218-288		

Subjects in this clinical investigation shall be referred to as “subjects.” For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and MTD determination and may be replaced by an additional subject at that same dose level, as necessary, to ensure that all dose escalation decisions are made with sufficient safety data (eg, safety data from at least 3 evaluable subjects in a multi-subject cohort).

Subjects who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs may be replaced at the discretion of the Medical Monitor or DLRT.

5.2.2 Number of Sites

Approximately 40 investigative sites in North America, Europe, Asia and Australia will be included in the study. Additional sites and countries may be added. Sites that do not enroll subjects within 4 months of site initiation may be closed.

5.3 End of Study

5.3.1 End of Study Definition

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

The primary completion date is the date when data for the primary endpoint are last collected for the purposes of conducting the primary analysis.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study 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), following any additional parts in the study (eg, long-term follow-up), as applicable.

5.3.2 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for up to 3 years.

This includes a screening period lasting up to 28 days, a treatment period lasting until disease progression and a follow-up period lasting up to 3 years from the first dose of AMG 160. Treatment beyond disease progression may be allowed as per PCWG3 guidelines (Section 12.10; Scher, et al 2016).

The actual duration for individual subjects will vary depending upon tolerability of AMG 160, evidence of clinical progression, and willingness to participate in the study.

End of study for an individual subject is defined as the date of the final study visit when assessments and/or procedures are performed.

5.4 Justification for Investigational Product Dose

The PK of AMG 160 in humans was estimated using allometric scaling of PK parameters obtained from nonclinical studies [redacted]

The planned doses of AMG 160 in this study are 0.003, 0.01, 0.03, 0.09, 0.15, 0.3, 0.6, 0.9, [redacted] mg, and higher administered as a planned 3-day eIV infusions (with the option to modify to range from 2-day to 7-day infusion starting cycle 1 day 1 only) or short term infusions (approximately 60 minutes) in subjects with mCRPC.

As recommended by the FDA, the selection of the starting dose for this first-in-human study was based on the Minimum Anticipated Biological Effect Level (MABEL) for BiTE® molecules (Saber et al, 2017). This was identified as the half maximal effective concentration (EC_{50}) of the most sensitive marker of AMG 160 activity in the most sensitive target expressing cell line. A starting dose of 0.003 mg was selected based on human PK prediction and is predicted to generate maximum serum concentrations equivalent to the MABEL. The use of the in vitro EC_{50} as the MABEL and basis for the first-in-human starting dose is supported by the previous and safe implementation of this strategy to identify the maximum recommended starting doses of previous BiTE molecules in clinical development.

[redacted]

However, the dosing schedule and DLRM decisions will be guided primarily by the safety and tolerability of AMG 160. In addition, prophylactic treatment with corticosteroids (and

additional prophylactic treatment in Part 3) and/or the implementation of step dosing regimens will be used to mitigate further risk of adverse events from AMG 160 activity (eg, CRS).

[redacted]

Planned dose levels for extended IV infusion approach:

The planned dose levels for eIV infusion are the same as those originally described in this study (Table 7-2). The starting dose level for C1D1 eIV infusion approach will be 0.03 mg infused over a period of 72 hrs. This will be followed by 60-minute IV infusions of target dose of AMG 160 on C1D8 and every 2 weeks thereafter (starting with the highest target dose level that has been deemed safe and tolerable in the ongoing study) (Section 2.2).

The starting dose for C1D1 eIV infusion of 0.03 mg infused over 72 hours is selected based on 0.01 mg as the current C1D1 step dose infused over 60 minutes (deemed safe

[redacted]

recommend modifying the dose or modifying the C1D1 eIV infusion time up to 7 days based on emerging safety and PK data.

Part 2 only:

The starting dose for AMG 160 will be 1 dose level below the dose level that is deemed to be safe and well tolerated in the ongoing AMG 160 monotherapy study (Part 1). Pembrolizumab will be dosed [redacted] with a maximum treatment duration of 2 years. Dose and exposure-response relationship studies have suggested that the [redacted]

[redacted]

Part 3 only:

[redacted]

AMG 160 will be administered at the MTD, RP2D, or highest dose level deemed safe and tolerable from Part 1.

[redacted]

Part 6 only:

Each subject will receive a single oral dose of all components of the CYP phenotyping cocktail [redacted] one day prior to cycle 1 day 1 and subsequently on cycle 2 day 1. This commonly used cocktail will utilize approved doses for each component.

AMG 160 will be administered at the MTD/RP2D as determined in Part 1.

5.5 Patient Input on Study Design

There was no patient input on study design.

6. 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 12.3).

6.1 Inclusion Criteria

All Parts

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

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

102 Age ≥ 18 years at the time of signing the informed consent

103 Subjects with histologically or cytologically confirmed mCRPC who are refractory to a novel antiandrogen therapy (abiraterone, enzalutamide, and/or apalutamide) and have failed at least 1 (but not more than 2) taxane regimens (or who are deemed medically unsuitable to be treated with a taxane regimen or have actively refused treatment with a taxane regimen). Progression on novel antiandrogen therapy may have occurred in the non-metastatic CRPC setting.

[redacted]

104 Subjects must have undergone bilateral orchiectomy or must be on continuous ADT with a gonadotropin releasing hormone (GnRH) agonist or antagonist

105 Total serum testosterone ≤ 50 ng/dL or 1.7 nmol/L

106 Evidence of progressive disease, defined as 1 or more PCWG3 criteria:

- PSA level ≥ 1 ng/mL that has increased on at least 2 successive occasions at least 1 week apart
- nodal or visceral progression as defined by RECIST 1.1 with PCGW3 modifications
- appearance of 2 or more new lesions in bone scan

107 Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 1

108 Life expectancy ≥ 6 months

[redacted]

[redacted]

6.2 Exclusion Criteria

All Parts

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

Disease Related

[redacted]

203 Central nervous system (CNS) metastases, leptomeningeal disease, or spinal cord compression

Other Medical Conditions

[redacted]

205 Active autoimmune disease or any other diseases requiring immunosuppressive therapy while on study

[redacted]

[redacted]

211 Myocardial infarction, unstable angina, cardia arrhythmia requiring medication, and/or symptomatic congestive heart failure (New York Heart Association > class II) within 12 months of first dose of AMG 160

[redacted]

Prior/Concomitant Therapy

215 Prior PSMA-targeted therapy (subjects on prior PSMA radionuclide therapy may be eligible if discussed with Amgen medical monitor prior to enrollment. [redacted]

216 Any anticancer therapy or immunotherapy within 4 weeks of start of first dose, not including LHRH/GnRH analogue (agonist/antagonist). Subjects on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to enrollment are eligible

217 Needing chronic systemic corticosteroid therapy (prednisone dose > 10 mg per day or equivalent) or any other immunosuppressive therapies (including anti-TNFα therapies) unless stopped 7 days prior to dosing

[redacted]

Part 2 only - subjects are excluded from this study if any of the following additional criteria apply:

[redacted]

226 Subjects on a prior PD-1 or PD-L1 inhibitor who experienced a grade 3 or higher immune-related adverse event prior to first day of dosing

227 History or evidence of interstitial lung disease or active, non-infectious pneumonitis

[redacted]

Part 3 only – subjects are excluded from this cohort if any of the following additional criteria apply:

229 Evidence of active tuberculosis on chest radiograph within 3 months prior to the first dose of investigational product (subjects receiving etanercept prophylaxis only).

[redacted]

6.3 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 (ICF), and all other subject information and/or recruitment material, if applicable (see Section 12.3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

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

Each subject who enters into the screening period for the study (defined 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.

6.4 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, medical history, prior therapies, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Refer to Section 9.1.1.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, 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.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of treatment shown in Table 7-1 below.

7.1 Treatment Procedures

7.1.1 Investigational Products

7.1.1.1 AMG 160 and Pembrolizumab

Table 7-1. Study Treatment

Study Treatment Name	Amgen Investigational Product:[a] AMG 160 (All Parts)	Non-Amgen Investigational Product:[b] Pembrolizumab (Part 2 Only)
Dosage Formulation	[redacted]	
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency		

Page 1 of 4

Footnotes are defined on last page of the table

Table 7-1. Study Treatment

Study Treatment Name	Amgen Investigational Product:[a] AMG 160 (All Parts)	Non-Amgen Investigational Product:[b] Pembrolizumab (Part 2 Only)
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency (continue)	[redacted]	
Route of Administration		
Accountability		
Dosing Instructions		

Page 2 of 4

Footnotes are defined on last page of the table

Table 7-1. Study Treatment

Study Treatment Name	Amgen Investigational Product:[a] AMG 160 (Parts 1, 2, 3, and 6)	Non-Amgen Investigational Product:[b] Pembrolizumab (Part 2 Only)
Hospitalization Guidance	[redacted]	Same as AMG 160

Page 3 of 4

Footnotes are defined on last page of the table

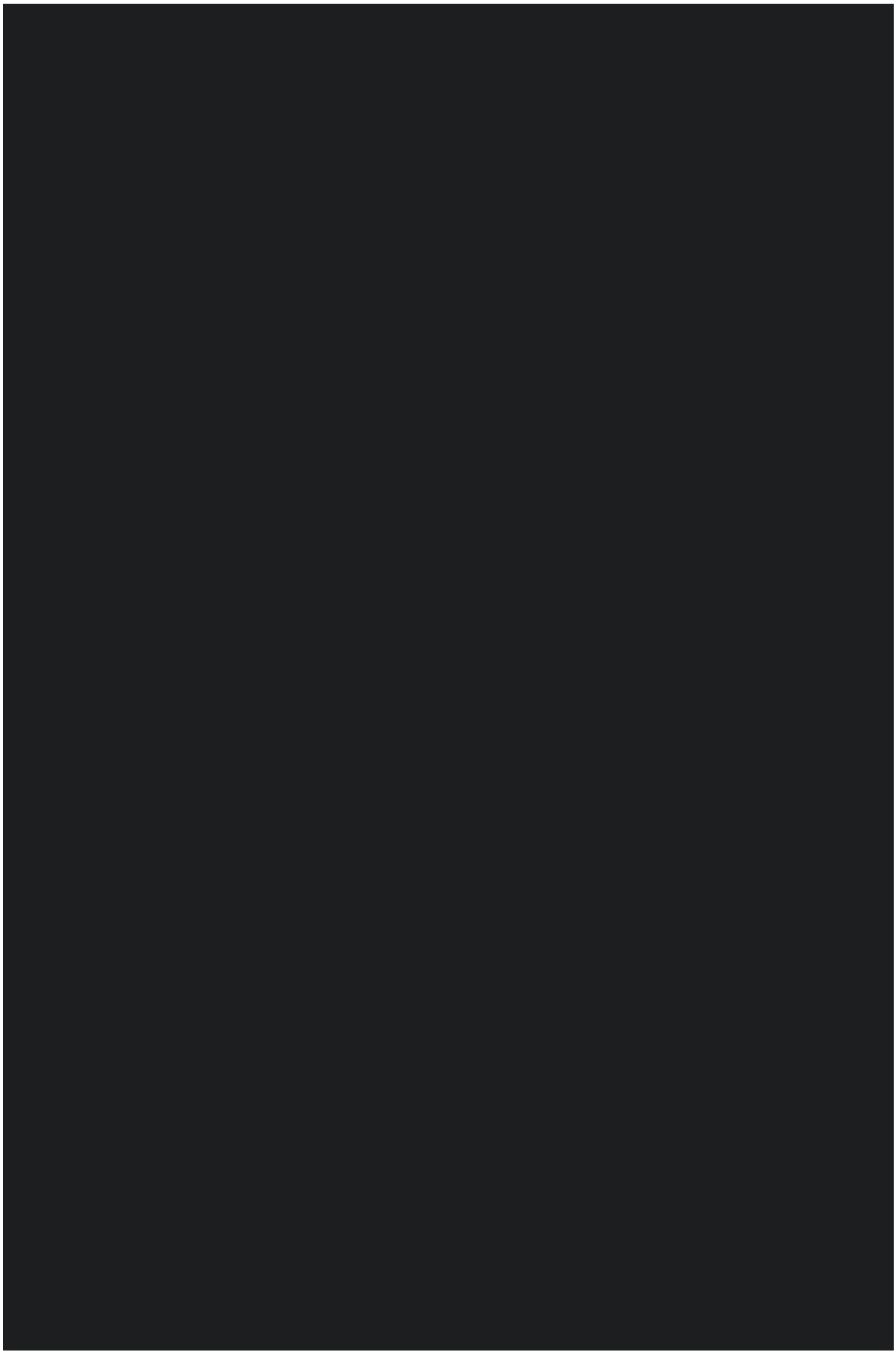
Table 7-1. Study Treatment

Study Treatment Name	Amgen Investigational Product:[a] AMG 160 [redacted]	Non-Amgen Investigational Product:[b] Pembrolizumab (Part 2 Only)
Monitoring Guidance	[redacted]	Not applicable

Page 4 of 4

[redacted]

[redacted]



[redacted]

Based on assessment by the DLRT and review of the available safety data, more than 1 incrementally increasing step doses may be implemented before delivering the target dose. Recommendations to implement more than 1 dose step(s) (sequentially or simultaneously) will be made by the DLRT and decision by Amgen will be communicated to the IRB/IEC, as appropriate.

[redacted]

Throughout the course of this study, one-step, two-step, and three-step dosing have been investigated, but are no longer being pursued.

[redacted]

[redacted]

7.1.1.4 Part 3 Only: Amgen Investigational Product: Etanercept

In Part 3, etanercept will be administered as prophylaxis for AMG 160-related CRS. Note, in some regions, this product is not commercialized by Amgen. Etanercept will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

Dosage formulation: Etanercept [redacted] in a single-dose vial is clear and colorless, sterile preservative-free solution, and is formulated at pH 6.3 ± 0.2. The solution includes L-arginine hydrochloride, sodium chloride, and sucrose.

[redacted]

Accountability: The planned dose, dose received, start date/time, stop date/time, and lot number of investigational product are to be recorded on each subject's CRF(s).

Dosing instructions: Refer to "Instructions for Use" as part of regional prescribing information.

7.1.1.5 Non-Amgen Investigational Imaging Products

^{68}Ga-PSMA-11 and ^{18}F-FDG (in some countries/regions when used for prostate cancer) are non-Amgen investigational products administered as part of PET/CT imaging assessments in this study.

7.1.2 Non-investigational Products

There are no non-investigational products in this study.

[redacted]

7.1.4 Other Protocol-required Therapies

All other protocol-required therapies, including glucocorticoids and tocilizumab**/siltuximab**, that are commercially available are not provided by Amgen

(except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies. **Sites are required to have tocilizumab or siltuximab (if tocilizumab is not available) on site for potential treatment of CRS.** [redacted]

7.1.4.1 Premedication

- Dexamethasone 8 mg PO (or equivalent dose of other corticosteroids) will be administered 6-16 hours prior to all doses of AMG 160 in cycle 1. Additionally, dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) will be administered within 1 hour prior to all doses of AMG 160 in cycle 1. [redacted] DLRT may modify premedication dosing regimen based on emerging safety data.
- [redacted]
- Per investigator discretion, prophylactic IV hydration (eg, 1 liter normal saline administered over 4-5 hours) should be given in cycle 1:
  - immediately after AMG 160 short-term (60 minute) infusions
  - after the start of C1D1 eIV infusion on day 1 on a different IV line
- Additional premedication with antihistamines, antipyretics, and/or anti-emetics are allowed, refer to Section 7.8.2.1.

The DLRT may recommend additional premedication including acetaminophen (eg, 975 mg PO single dose) and/or tocilizumab (4-8 mg/kg IV single dose) **(or siltuximab if tocilizumab is not available)** prior to or immediately after AMG 160 doses in cycle 1 and beyond.

7.1.4.2 Part 6 Only: Modified Cooperstown 5+1 CYP Phenotyping Cocktail

In Part 6, each subject will receive a single oral dose of all components of the CYP phenotyping cocktail [redacted]

[redacted] one day prior to cycle 1 day 1 (~24 hours prior to first AMG 160 infusion) and subsequently on cycle 2 day 1 (immediately following AMG 160 infusion).

7.1.5 Other Treatment Procedures

There are no other treatment procedures in this study.

7.1.6 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 and 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 product(s) provisioned and/or repackaged/modified by Amgen (ie, AMG 160 and etanercept). [redacted]

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

[redacted]

7.1.7 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:

[redacted]



7.2 Method of Treatment Assignment

Subjects who meet eligibility criteria will be assigned to treatment with AMG 160.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 AMG 160 Dose Determination and Dose Modification

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

7.4.1.1 Dose-exploration Phase

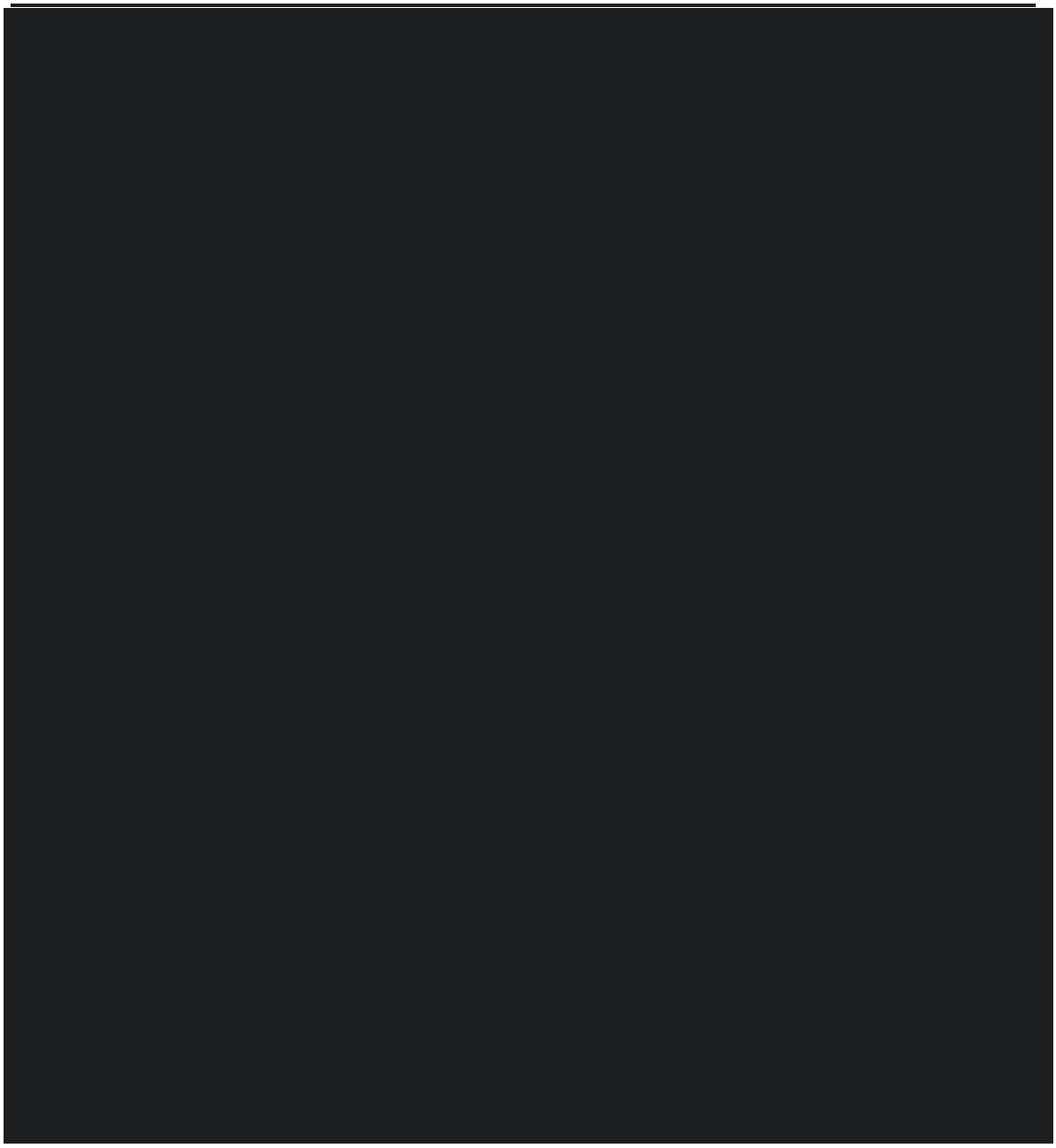
The Part 1 dose-exploration phase of the study will enroll up to 90 subjects with mCRPC. Table 7-2 and Table 7-3 describes the planned dose levels for investigation in step dose and eIV cohorts, respectively. Dose exploration will be conducted in 2 stages: single-subject cohort(s) followed by multiple-subject cohort(s) (3 to 4 subjects per cohort).

The Part 2 dose-exploration phase of the study will enroll up to **3**0 subjects with mCRPC in multiple subject cohorts only (3 to 4 subjects per cohort). The starting dose for AMG 160 will be 1 dose level below the dose level that is deemed to be safe and well tolerated in the ongoing AMG 160 monotherapy study (Part 1). Pembrolizumab will be

dosed [redacted] with a maximum treatment duration of 2 years. See Table 7-4 for AMG 160 dose levels in Part 2.

The planned AMG 160 dose levels for Part 3, Part 6, and the [redacted] cohorts are shown in Table 7-5 and Table 7-6.

[redacted]



7.4.1.1.1 Single-subject Cohorts

Part 1 only

The starting dose will be based on the MABEL (Saber et al, 2017). Dose exploration will begin with single-subject cohort(s). The starting dose is expected to have a maximum serum concentration similar to that of the MABEL. This serum concentration is expected to be lower than those at which treatment-related adverse events or efficacy is predicted to be observed.

If the subject does not experience a clinically significant treatment-related grade 2 adverse event or DLT (Section 7.4.1.3) during the initial 28 days of treatment

(DLT window), then the next subject may be dosed at the next higher dose level(s) per Table 7-2. A formal DLRM will not be convened if no DLTs are reported in single subject cohorts (all safety data will be reviewed prior to a dose escalation decision). The DLRT may also convene ad hoc meetings any time to review safety data if deemed necessary.



NOTE: See Sections 12.12 and 12.13 for CRS and TLS grading criteria.

7.4.1.1.2 Multiple-subject Cohorts

Part 1

Part 1 dose escalation in multiple-subject cohorts (3-4 subjects per cohort) will begin as described in Section 7.4.1.1.1 and follow the planned schedule shown in Table 7-2. Enrollment of the first 2 subjects in a given dose level will be staggered by at least 3 days. The DLRT will convene to review the safety data and recommend the appropriate dose to be implemented. The DLRT may recommend to enroll more subjects for safety reasons at any point during the study. DLRT may also recommend opening 2 or more cohorts at a given dose level (eg, involving different dose steps) simultaneously. For multiple-subject cohorts, the DLRT will not recommend dose escalation decisions until at least 3 of the subjects in the cohort received the full planned dose for the first cycle and have been followed for safety events for a minimum of 28 days from the first dose of AMG 160 (except if a subject experienced a DLT).



If late onset adverse events (ie, after the 28-day DLT period) occur during a cohort, the DLRT may adaptively re-consider the doses evaluated within a cohort for subsequent

dosing and/or possibly trigger a de-escalation or withholding of additional doses in subsequent cohorts. Based on the BLRM model and after reviewing all available safety and tolerability data, the DLRT may recommend dosing at intermediate dose levels between the planned dose levels in Table 7-2 or at a max dose above the planned max dose.

Dose escalations will end once any of the following events occur:

[redacted]

To acquire additional safety [redacted] data to better fully inform the RP2D, additional subjects may be enrolled at a dose level that has been shown to not exceed the MTD based on the dose-escalation criteria described above, and at which there is evidence of anti-tumor activity and/or [redacted] modulation. Up to approximately 3 additional subjects per dose level may be enrolled.

Additional subjects (up to 20 subjects) may be enrolled in 1 or more monotherapy dose levels that have been shown to be safe and tolerable which is defined as backfill enrollment. This backfill enrollment will be done to better estimate the RP2D and better characterize the safety, efficacy, PK, and pharmacodynamics for AMG 160 monotherapy and may be concurrent with dose escalation to identify the MTD.

[redacted]

[redacted]

Part 2

In Part 2 (AMG 160 Combination with Pembrolizumab), dose escalation/de-escalation decisions in multiple-subject cohorts will be guided by the modified toxicity probability interval design (mTPI-2). The MTD is the dose level predicted to have the highest probability of a DLT rate within the target interval of [redacted]% to [redacted]%. Subjects will be enrolled in multiple-subject cohorts (3-4 subjects per cohort). Based on review of safety and available pharmacokinetic data of at least 3 subjects through 28 days from start of pembrolizumab (DLT period), the DLRT may recommend escalation to the next higher dose level of AMG 160 in combination with the fixed dose of pembrolizumab.

Dose reductions due to safety would occur with AMG 160 dose. Pembrolizumab dose can be held for safety reasons due to toxicities attributed to its use. Refer to Section 2.2 for schedule of assessments. Dose escalation will end upon determination of the MTD and/or RP2D for the AMG 160 plus pembrolizumab combination.

See Section 12.16 for additional information.

Parts 1 and 2

Determination of whether a subject is evaluable for DLT assessment will be made in accordance with the following rules:

[redacted]

Intra-subject Dose Escalation

Part 1 and Part 2 subjects who complete the DLT period may proceed to a higher dose level in a subsequent treatment cycle once that dose cohort has been deemed safe after consultation with the principal investigator and sponsor, as long as no DLT has been reported for this subject during or after completion of the DLT period. See Table 2-6 for additional PK assessments during intra-subject dose escalation. Additional assessments may be performed as needed upon consultation between the investigator and medical monitor.

7.4.1.2 Dose-expansion Phase

In Part 1 (AMG 160 Monotherapy), once the MTD or RP2D has been selected based on dose-exploration phase, enrollment will commence in the dose-expansion phase to confirm the safety and tolerability of the selected dose and to further evaluate pharmacodynamics and anti-tumor activity. It is anticipated that approximately 50 subjects will be enrolled in the expansion phase for a particular dose level, subject selection approaches, or dosing schedule selected for expansion.

Dose expansion 1a will enroll approximately 50 subjects, independent of PSMA status. Dose expansion 1b will enroll approximately 50 subjects [redacted]

Interim safety analyses will be done after an initial 10 subjects have been treated at MTD or RP2D (including subjects treated in the dose escalation and dose expansion [no earlier than 28 days after the tenth subject has been administered AMG 160]). The DLRT may also convene ad hoc meetings any time to review safety data if deemed necessary. Based on these interim safety results and reviewing an update to the BLRM estimate of the MTD using all available data including data from dose exploration and expansion subjects, the DLRT may recommend to modify the dose level and/or schedule of treated subjects. A final BLRM estimate of the MTD will use all data from dose exploration and dose expansion.

[redacted]

[redacted]

7.4.1.3 Dose-limiting Toxicity

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Section 12.4, with the exception of CRS, which will be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 12.12), TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 12.13), and ICANS will be using the criteria referenced in the publication by Lee et al (2019) (see Section 12.14). Fever, hypotension, hypoxia, transaminitis and other signs/symptoms attributed to CRS will be reported as CRS based on the CRS grading scale (Table 7-7).

Dose-limiting toxicities are defined as any adverse event with an onset within first 28 days following first dose of AMG 160 monotherapy (Part 1) or in combination with

pembrolizumab (Part 2) with any of the following criteria unless clearly attributable to causes other than AMG 160 treatment:



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

7.4.2.1 Amgen Investigational Product: AMG 160

The reason for dose change of AMG 160 is to be recorded on each subject's CRF(s).

7.4.2.2 Non-Amgen Investigational Product: Pembrolizumab

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

7.4.2.3 Infusion Interruptions/Delays/Withholding and Re-start in Case of Technical/Logistical Issues

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

Infusion Interruptions due to Technical/Logistical Issues

The administration of AMG 160 should not be interrupted for short-term (60 minute) or eIV infusions, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible, and the infusion continued at the earliest time possible.

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

- 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 (60 minute) 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 2.2) or the cycle day on which the original (interrupted) infusion was administered. Premedication as described in Section 7.1.4 for treatment cycle 1 should be administered. If the infusion will need to be withheld, follow the instructions for re-start after interruptions due to adverse events described below for the next infusion.

For eIV (2-7 day) infusions, if an infusion interruption occurs due to reasons other than adverse events (eg, technical or logistic reasons) and does not exceed 24 hours, the infusion can be restarted at the same dose without additional measures. If the interruption exceeds 24 hours, the restart of the infusion should be performed in the hospital or clinic under the supervision of the investigator or designee and premedication as described in Section 7.1.4 for treatment cycle 1 should be administered. Refer to IPIM for details of handling, preparation, and administration of eIV infusions.

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 14 ($\pm$ 1) days; eg, if the day 8 infusion needs to be delayed for logistical issues, and could only be administered on day 10, the next infusion should be administered on day 24 ($\pm$ 1 day) rather than the regular day 22. The $\pm$ 1-day window is allowed until the original dosing schedule is met again.

If the delay of the next infusion was 7 days, the dose will need to be skipped and the instructions for re-start after interruptions due to adverse events described below should be followed.

7.4.2.4 Infusion Interruptions/Delays/Withholding and Re-start due to Adverse Events

7.4.2.4.1 General Guidelines

Subjects should be assessed for toxicity before each infusion of AMG 160. The severity of the toxicity will be graded using the CTCAE version 5.0 (Section 12.4), with the exception of CRS, which must be graded using the criteria referenced in the publication by Lee et al, 2014 (see Section 12.12), TLS, which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al, 2008) (see Section 12.13), and ICANS will be using the criteria referenced in the publication by Lee et al (2019) (see Section 12.14). Infusion modification and dose reduction due to a toxicity will be performed according to the instructions described below and outlined in Table 7-9.



7.4.2.4.2 Infusion Interruptions due to Adverse Events

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

Events requiring an infusion interruption are listed in Table 7-9.

7.4.2.4.3 Delay of Subsequent Infusion due to Adverse Events

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

Events requiring a delay of the subsequent infusion are listed in Table 7-9.

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

7.4.2.4.4 Re-start of infusion

Re-starting treatment after an interruption/delay due to an adverse event or if the interruption/ delay was 7 days, regardless of the reason, should be performed under medical supervision. Premedication as described in Section 7.1.4 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 for days 1, 2, and 3 per the Schedule of Activities for cycle 1 (Section 2.2).

- 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 at least 48 hours after re-start of the infusion.

7.4.2.4.5 Dose Adjustments and Re-start at a Lower Dose Level

For adverse events for which restart of treatment is allowed according to the guidelines outlined in Table 7-9, treatment may be resumed at the same or lower dose.

Re-start at a lower dose level:

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

- If the event occurred during the infusion and caused an interruption of the infusion for more than 7 days and therefore the affected dose was withheld, or
- If the event started after the end of an infusion and administration of the next infusion had to be delayed for more than 7 days due to the event.
- For specific events as outlined in Table 7-9.

In either case, re-escalation to the target dose can be considered for the next infusion if treatment at the lower dose has been well tolerated with no events requiring dose interruption or delay as described in Table 7-9. After the dose re-escalation, the

following assessments should be performed as for day 8 through day 11 per the Schedule of Activities for cycle 1 (Section 2.2).

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

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

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

Part 2 only

For treatment interruptions, delays, and discontinuations related to AMG 160 in combination with pembrolizumab, refer to AMG 160 monotherapy instructions in Table 7-9 in consultation with the Amgen medical monitor. If restarting AMG 160 plus pembrolizumab due to adverse events, dose reductions would occur with AMG 160 (as described in Section 7.4.2.4.5) while keeping pembrolizumab dose constant. However, pembrolizumab can be held for safety reasons due to toxicities attributed to its use or if subjects experienced grade 3 or higher adverse events on C1D1 administration of AMG 160.

If any of the following events occur in Part 2, further accrual will be suspended and a safety analysis conducted and submitted to FDA for review prior to resuming enrollment.

[redacted]

Part 3 Only

Refer to regional prescribing information for details regarding dose modification for etanercept (Part 3)



























[redacted]

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product other protocol-required therapies during the study are provided in the IPIM.

7.6 Treatment Compliance

AMG 160, pembrolizumab, and etanercept will be administered at the study center by a qualified staff member. A physician must be available at the time of administration of investigational product. Information regarding investigational product administration including date, time, dose, start and stop time of infusion, and other essential information are to be recorded on the individual subject's Investigational Product Administration CRF per the CRF completion guidelines.

For protocol-required treatment administered at home ([redacted]), a diary will be provided to subjects at the beginning of each cycle and the study staff will provide guidance to the subjects on how to complete the diary. The site will review the diary on day 1 of the next cycle and end of treatment visit.

Please refer to IPIM for more details on treatment compliance.

7.7 Treatment of Overdose

The effects of overdose of this product are not known.

The administered AMG 160 monotherapy or in combination with pembrolizumab 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 12.4.

A dose of > 10% higher than the intended AMG 160 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 12.4.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were taken/used from 3 months prior to signing informed consent will be collected. Collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

For all prior therapies taken for prostate cancer (eg, chemotherapy or hormonal 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
- type of progression (biochemical [ie, a rising PSA], radiographic, and/or symptomatic)
- response (resistant versus sensitive): categorized on the basis of the post-therapy PSA or radiographic change pattern for agents that reduce tumor burden

  NOTE: A taxane regimen is defined as a minimum exposure of 2 cycles of a taxane.

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). Details of prior radioisotope therapy should also be recorded.

7.8.2 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 7.1.7.

Concomitant therapies are to be collected from informed consent through the end of safety follow-up period.

For concomitant therapies being taken for the disease under study (eg, pain medication), collect therapy name, indication, dose, unit, frequency, start and stop dates. For all

other concomitant therapies, including vaccines, collect therapy name, dose, start and stop dates.

7.8.2.1 Supportive Care

Subjects can receive supportive care according to local guidelines for blood product support, antibiotics, antivirals, analgesics, antipyretics, etc. Details of supportive care measures should be recorded for patients in dose expansion phase.

7.8.2.2 Bone Disease Therapy

Treatment of prostate bone disease, hypercalcemia, and bone pain should be done according to institutional standards. This may include concurrent treatment with bisphosphonates or denosumab. Radiotherapy for palliative care such as bone pain is permitted after discussion with Amgen medical monitor and details should be recorded for patients in dose expansion phase.

7.8.2.3 Growth Factors

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

7.8.2.4 Tumor Lysis Syndrome

While rare in prostate cancer, TLS is a severe, life-threatening disorder that can occur in highly proliferative malignancies or with debulking of extensive tumor burden. Tumor lysis syndrome is characterized by a group of metabolic disorders caused by the massive and abrupt release of cellular metabolites into the blood including lactase dehydrogenase, uric acid, phosphorus, potassium, and calcium after lysis of the malignant cells (Coiffier et al, 2008). The metabolic complications predispose patients with cancer to various clinical complications included renal failure, seizures, cardiac arrhythmias, and even sudden death. To allow for early diagnosis, all subjects must be monitored closely for laboratory and clinical evidence of a possible TLS as outlined in Section 12.13.

To prevent TLS, ensure all subjects are well hydrated and provided supportive care measures before administration of AMG 160. To prevent TLS, before administration of AMG 160 monotherapy or in combination with pembrolizumab all subjects should receive, at the discretion of the investigator, appropriate hydration and supportive

measures according to local standard of care and institutional guidelines. Monitor for evidence of TLS during treatment and manage promptly including interruption of AMG 160 infusion as outlined in Table 7-9. Subjects who experience TLS should be managed according to the local standard of care and institutional guidelines.

7.8.2.5 Nausea, Vomiting, and Diarrhea

The causes of nausea, vomiting, and diarrhea in subjects with cancer can be multifactorial. Therefore, a careful assessment which includes a detailed history, physical examination, and investigations for causes is vital. Management of nausea, vomiting, and diarrhea should be tailored to the individual subject's clinical situation.

7.8.2.5.1 Nausea and Vomiting

Antiemesis prophylaxis may be given according to local standard of care institutional standards if clinically indicated at the investigator's discretion. Treatment of nausea and vomiting with antiemetics such as metoclopramide should be considered according to the local standard of care and institutional guidelines. In cases with nausea and vomiting lasting for > 24 hours, additional treatment with corticosteroids (dexamethasone or prednisolone) should be considered depending on tolerability/duration of previous dexamethasone administration.

7.8.2.5.2 Diarrhea

All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid, and electrolytes should be substituted via IV infusion. Consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.

Treatment with loperamide (starting dose of 4 mg, followed by 2 mg every 2 hours) should start after occurrence of the first episode of diarrhea. In cases with diarrhea lasting for > 24 hours, additional treatment with corticosteroids (dexamethasone or prednisolone) should be considered depending on tolerability/duration of previous dexamethasone administration. Additional work-up and/or GI consultation may be considered, as needed.

7.8.2.6 Vaccines

The use of vaccines will be allowed during therapy per regional and institutional standard of care. Every effort should be made to complete SARS-CoV-2 vaccinations prior to 14 days from first dose of AMG 160. SARS-CoV-2 vaccinations are not allowed during screening (within a minimum of 14 days from first dose of AMG 160) and in the first

treatment cycle for better assessment of safety parameters. Throughout the study, SARS-COV2 vaccination should be avoided within 3 days after the administration of AMG 160 due to the potential of CRS development. In the event where a subject requires steroids for CRS prophylaxis or treatment of adverse events, vaccination should be avoided while on steroids.

8. Discontinuation Criteria

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 Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 2.2) 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 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.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3.

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

- decision by sponsor
- lost to follow-up
- death
- ineligibility determined
- protocol deviation
- non-compliance
- adverse event
- subject request
- no longer clinically benefitting (may include clinical deterioration [disease or therapy related] or need for a change in systemic therapy; Scher et al, 2016)
- protocol-specified criteria:



8.2 Discontinuation 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.

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 12.6 for further details). Refer to the Schedule of Activities (Section 2.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

Not applicable to this study.

8.2.2 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

8.3 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 can 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.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (Section 2.2). As protocol waivers or exemptions are not allowed 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.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

The procedures to be completed during screening are indicated in the Schedule of Activities (Section 2.2). 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 ICF, the site will register the subject manually 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 6.4) 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 rescreening 1 time.

Rescreen subjects must first be registered as screen failures 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 ICF, all screening procedures, including informed consent with the exception of [redacted] PSMA PET and FDG PET scans, must be repeated.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Section 2.2).

On-study visits may be completed within ± 1 day (except for PK collections days) during cycles 1 and 2 and within ± 3 days cycle 3 onwards. The date of the first dose of

AMG 160 is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Assessments are done pre-infusion unless otherwise specified in the Schedule of Activities.

9.1.3 Safety Follow-up

The procedures to be completed during safety follow-up are indicated in the Schedule of Activities (Section 2.2). Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+ 3) days after the end of the last dose of AMG 160, or prior to initiation of other therapy, whichever occurs first.

9.1.4 Long-term Follow-up

The procedures to be completed during long-term follow-up are indicated in the Schedule of Activities (Section 2.2). Long-term follow-up will be conducted every 6 months up to 3 years from the first dose of AMG 160 monotherapy or in combination with pembrolizumab for all subjects who have not withdrawn consent by clinic visit, telephone or chart review to assess for survival and/or the commencement of subsequent cancer therapy.

9.1.5 End of Study

The end of study visit is defined as the date of the final study visit (eg, final long-term follow-up visit) when assessments and/or procedures are performed.

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 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.

9.2.1.2 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. Additionally, demographic data will be used to study the impact on biomarkers variability and **PK** of the protocol-required therapies.

9.2.1.3 Medical History

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

In addition to the medical history above, prostate cancer 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 grade will be collected for each condition that has not resolved.

9.2.1.4 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).

9.2.1.5 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.

[redacted]



9.2.1.8 Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes.

9.2.1.9 Performance Status

The subject's performance status will be assessed using the ECOG performance scale (see Section 12.9).

9.2.2 Efficacy Assessments

Efficacy will be determined by both clinical laboratory values and radiographic assessments (as outlined in Section 4.1).

Clinical Laboratory Values

Prostate-specific antigen 30/50/70/90 Response: defined as 30%, 50%, 70%, and 90% reduction in PSA Level

Circulating tumor cell Response: defined as CTC0 (reduction of CTCs $>$ 0 to 0) or CTC conversion ($\geq$ 5 CTCs/7.5 mL blood to $\leq$ 4 CTCs/7.5 mL blood)

Radiographic Assessments

Radiographic assessments will be obtained as scheduled in Table 2-7 irrespective of cycle duration including dose delays and treatment discontinuation.

Standard radiological assessments should take place until clinically significant disease progression or deterioration, withdrawal of consent, or start of new anticancer therapy. Every assessment must include the chest, abdomen, and pelvis, all other known sites of disease and magnetic resonance imaging (MRI) of the brain if a subject has signs or symptoms suggestive of CNS metastases. The MRI/CT can be obtained earlier if clinical deterioration necessitates an earlier scan at the discretion of the managing

physician. The same contrast and modality used at screening should be used for all subsequent assessments. ^{68}Ga-PSMA-11 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 be performed at baseline (and every 12 weeks for response assessment in the dose-expansion phase only). Imaging assessments have a ± 7-day window. The use of ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT (in some countries/regions for prostate cancer) is investigational. Both ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT scans are optional in [redacted]

Tumor burden assessments will be performed per PCWG3 guidelines (see Section 12.10 for details). To confirm disease progression (PD), a second MRI/CT scan must be performed at least 4 weeks after the first detection of radiographical progression. Responses (partial response [PR] and complete response [CR]) require confirmation by a repeat consecutive assessment at least 4 weeks after the first detection of radiographical response. Planar bone scintigraphy (for disease progression assessment) must be performed using conventional ^{99m}technetium methylene diphosphonate radionuclide (^{99m}Tc-MDP) or other equivalent ^{99m}Tc-labeled radiotracers. Confirmation of bone disease progression by bone scan should be performed as described (PCWG3 guidelines). Disease progression based on both MRI/CT and bone scans will be used in radiographic progression endpoints (eg, time to radiographic progression and radiographic PFS) evaluation. Soft-tissue progression based on MRI/CT scan will be used in response endpoints (eg, objective response and DOR) evaluation. Treatment beyond confirmed tumor progression may be allowed as per PCWG3 guidelines (Section 12.10; Scher et al, 2016). Refer to the imaging manual for details on imaging assessments.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities (Section 2.2).

9.2.3.1 Adverse Events

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

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Section 12.4. The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the

subject that occur after the first dose of investigational product(s) through the safety follow-up visit are recorded using the Events CRF.

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

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Events CRF as serious adverse events and recorded and reported per Section 9.2.3.1.1.3 and Section 12.4.

Disease-related events pre-defined for this study are listed in Section 12.11.

9.2.3.1.1.2 Adverse Events

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product(s) through the safety follow-up visit are reported using the Events CRF. Adverse events related to study-mandated procedures are collected from signing of the informed consent.

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Section 12.4, with the exception of CRS, which will be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 12.12) and TLS, which will be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 12.13), and ICANS will be using the criteria referenced in the publication by Lee et al (2019) (see Section 12.14).

[redacted]

9.2.3.1.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the **safety** follow-up **visit** are reported using the Events CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

If the investigator becomes aware of serious adverse events **suspected to be related to investigational products** after the protocol-required reporting period (as defined in Section 9.2.3.1.1.3) is complete, **then** these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event **using Events eCRF**.

As a study endpoint is overall survival, the investigator will also need to collect/report fatal serious adverse events (regardless of causality) to Amgen within 24 hours following investigator's awareness of the event.

After the End of Study, 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 products, then these serious adverse events will be reported to Amgen within 24 hours following the investigator's awareness of the event.

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

The method of recording, evaluating, and assessing causality of adverse events, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.2 Reporting a Safety Endpoint as a Study Endpoint

Safety endpoints (any fatal event occurring outside the protocol required reporting period) that are study endpoints are reported on the Events CRF. All endpoints that also meet the criteria of serious adverse event or serious disease related event must also be transmitted to safety within 24 hours of the investigator's knowledge of the event (refer to Section 12.4).

9.2.3.1.3 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to 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 inquire about adverse event occurrence.

9.2.3.1.4 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 8.3). Further information on follow-up procedures is given in Section 12.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Events CRF.

9.2.3.1.5 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 holding the relevant Investigational New Drug/Clinical Trial Application for either AMG 160 or ^{68}Ga-PSMA-11 has a legal responsibility to notify both the local

regulatory authority and other regulatory agencies about the safety of AMG 160 or ^{68}Ga-PSMA-11, 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.6 Pregnancy

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 AMG 160.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and is to follow the procedures outlined in Section 12.5. 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 12.5.

9.2.3.2 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.

[redacted]

After each AMG 160 monotherapy or in combination with pembrolizumab infusion for the first 2 cycles (during the 48-hour hospitalization or outpatient monitoring period), vital signs should be assessed accordingly during the following time points:



9.2.3.3 Pulse Oximetry

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

9.2.3.4 Electrocardiograms

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. ECGs should be performed in a standardized method, in triplicate, and run consecutively (ie, < 30 seconds apart), prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, QTc, RR, and PR intervals.

AMG 160 Monotherapy Dose Exploration and Expansion (Part 1 only):

- Screening: single ECG
- For cycles 1 and 2: triplicate ECGs at baseline and at time points after dosing

For cycle 3 and beyond: single ECGs may be collected per time point

Parts 2, 3, [redacted] and 6:

- All cycles: single ECGs collected per time point

Baseline is defined as the pre-dose assessment on cycle 1 day 1. The investigator or designated site clinician will review all ECGs. ECGs will be transferred electronically to an ECG central vendor and may be sent for analysis per Amgen instructions. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen. Standard ECG machines should be used for all study-related ECG requirements.

9.2.3.5 Vital Status

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

9.2.4 Clinical Laboratory Assessments

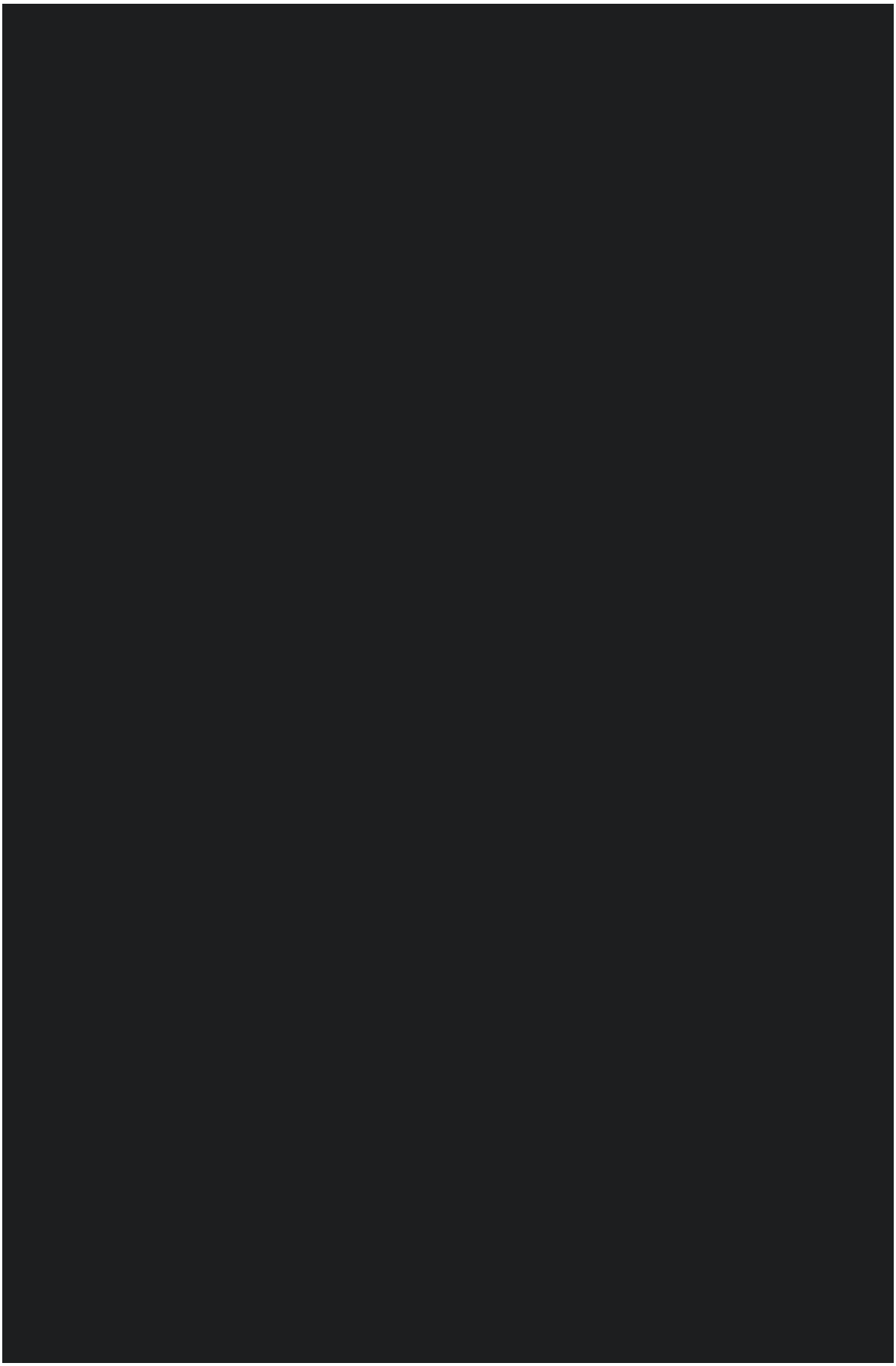
Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Section 2.2) for the timing and frequency.

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 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Section 2.2).

9.2.4.1 Pregnancy Testing

This is not relevant to this study as there are no female subjects.





9.2.5 Pharmacokinetic Assessments

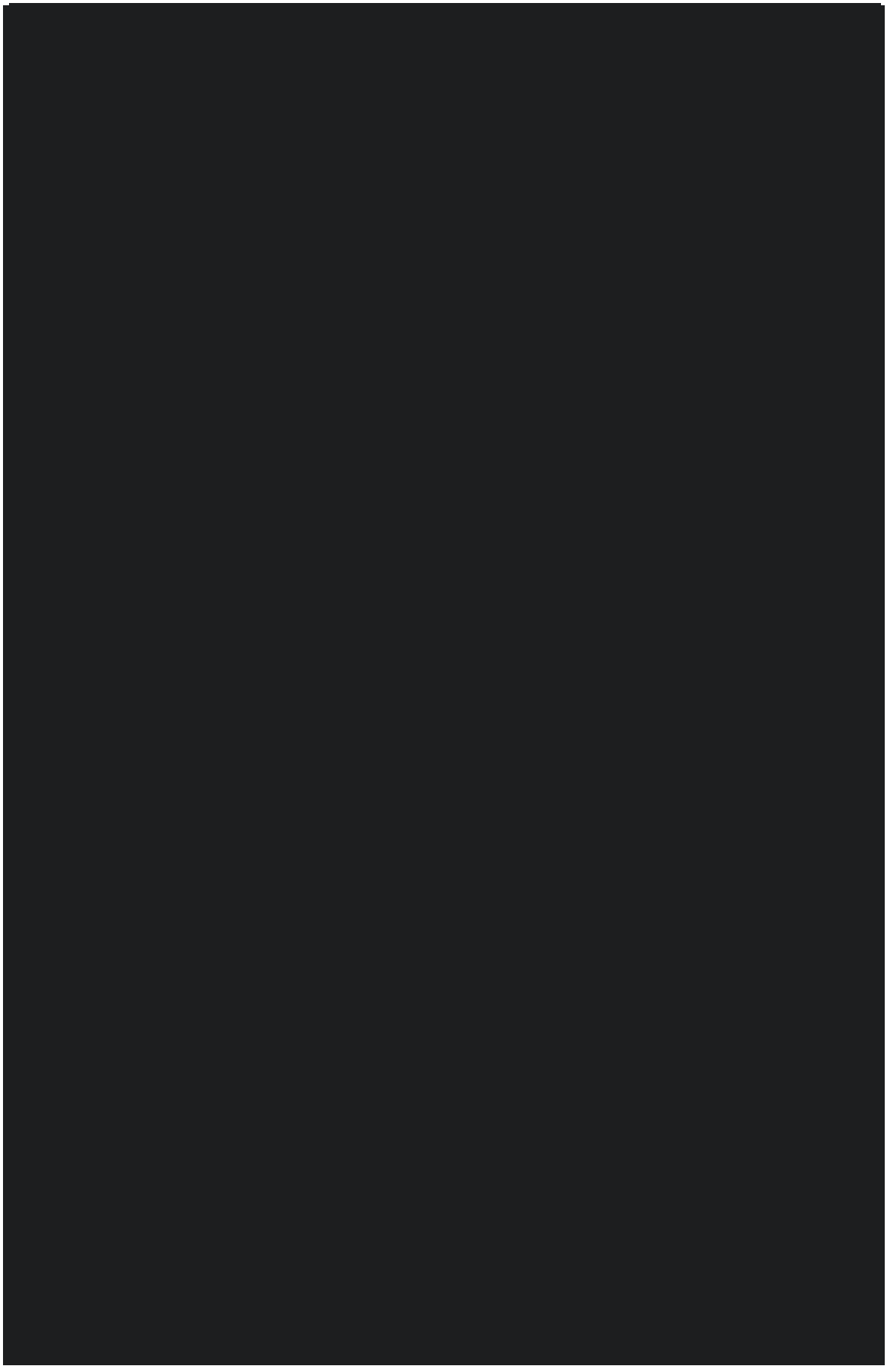
All subjects enrolled will have pharmacokinetic samples assessed. Blood samples of approximately 2.5 mL will be collected for measurement of serum concentrations of AMG 160 as specified in Table 2-6. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. 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.

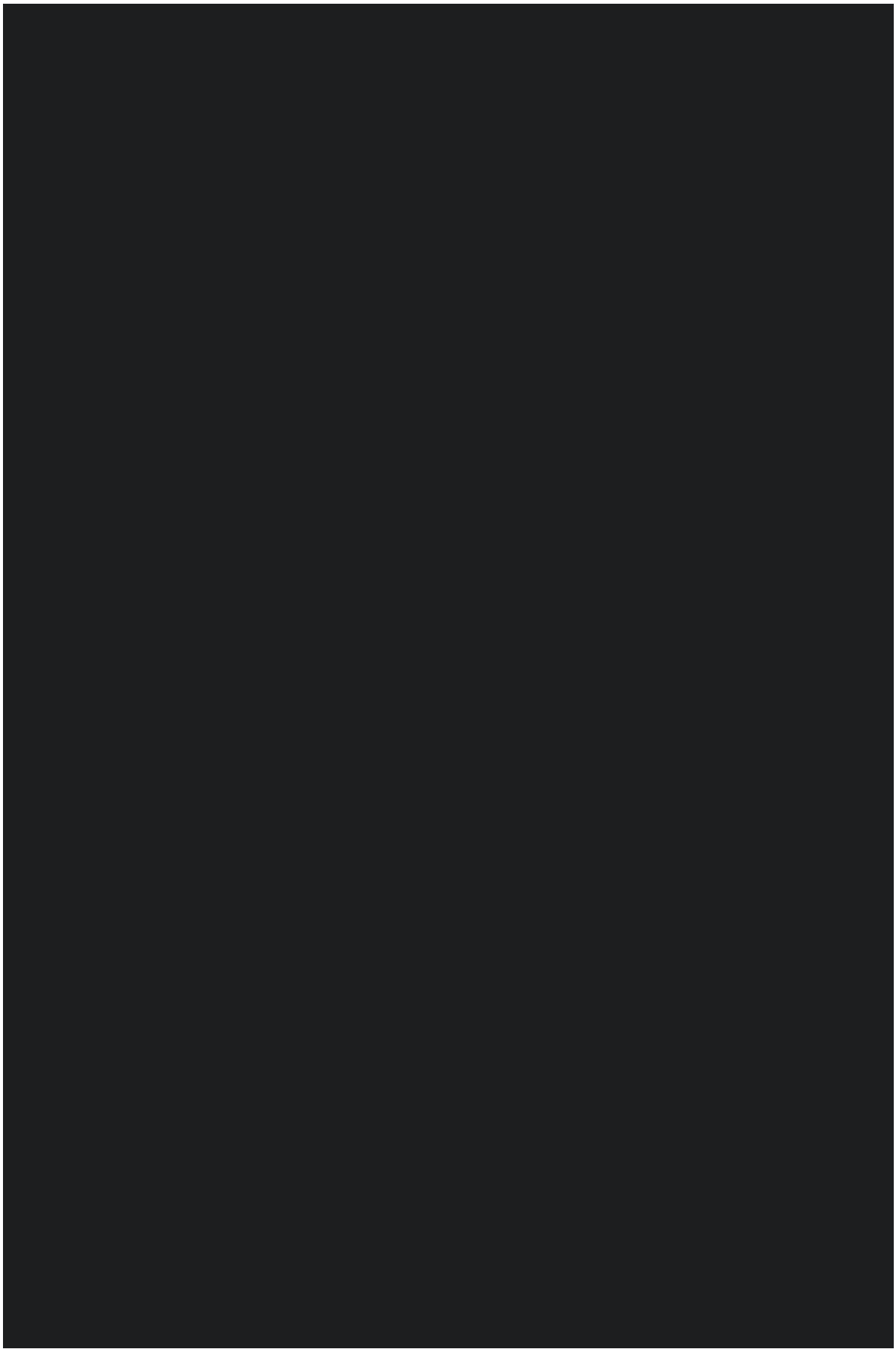
PK samples should be collected at the exact nominal time point as noted. If unable to collect a PK sample at the specified nominal time point collect it as close as possible to the nominal time point and record the actual collection time.

For Part 2, end of infusion PK Samples should be collected right after AMG 160 infusion and post-infusion flush and prior to pembrolizumab dosing.

For Part 6, 7 mL of total blood volume will be collected at the protocol defined time points to assess the plasma concentrations of CYP probe substrates. Two aliquots will be collected; 4 mL tubes with sodium heparin as the anticoagulant (for assay of [redacted]) and a 3 mL tubes with sodium EDTA as the anticoagulant (for assay of [redacted].

[redacted]





10. Statistical Considerations

10.1 Sample Size Determination

It is anticipated that approximately 218-288 subjects will be enrolled in this study. See Section 5.2 for detailed breakdown of sample size by part and cohort.

Part 1

The sample size in the dose-escalation phase is based on practical consideration and is consistent with conventional oncology studies with the objective to estimate the MTD. With 3-4 subjects in a cohort, there is a 27% to 70% probability of observing at least 1 DLT if the true DLT rate is 10% to 33% and with 6 subjects in a cohort, there is a 47% to 91% probability.

In the dose-expansion cohort, a subject number of 50 will provide a 92% probability of observing at least 1 adverse event with 5% incidence rate. An exact 95% binomial CI will be provided for overall response rate. With approximately 50 enrolled subjects, a two-sided 95% CI of objective response rate per RECIST 1.1 (PCWG3 modifications), ORR, will extend at most 23% in length from the observed ORR, ie, if the estimated ORR is 50%, the estimated 95% CI of ORR will be within (27%, 73%). This is assuming the true ORR is approximately 50% and the proportion of subjects with RECIST measurable disease is about 40%.

With 3 subjects at the initial safety review, there is a 27% to 70% probability of observing at least 1 DLT, if the true DLT rate is 10% to 33%. With 9 subjects, there is a 37% to 61% probability of observing a DLT, if the true DLT rate is 5% to 10%. Intensive pharmacokinetic sampling from combined 9 subjects will allow adequate characterization of AMG 160 **PK** in [redacted] subjects respectively.

Part 2

For Part 2 (AMG 160 Combination with pembrolizumab), sample size (n = 30) is based on practical considerations consistent with oncology studies with the objective to determine the MTD based on DLTs. With the total subject number of 20 treated at a combination, it will provide a 79% probability of observing at least 1 DLT with 5% incidence rate and 96% probability of observing at least 1 DLT with 10% incidence rate.

Part 3

For Part 3 (etanercept prophylaxis for AMG 160-related CRS), sample size (n = 20) is based on practical considerations consistent with oncology studies to determine

administering AMG 160 with etanercept prophylaxis only. With the total subject number of 20 treated at a combination, it will provide a 64% probability of observing at least 1 DLT with 5% incidence rate and 88% probability of observing at least 1 DLT with 10% incidence rate.



Part 6

For Part 6 (Cytochrome P450 [CYP] Cocktail Drug Interaction Cohort), sample size (up to 8) is based on practical considerations consistent with oncology studies. With the total subject number of 8 subjects treated at a combination, it will provide a 36% probability of observing at least 1 DLT with 5% incidence rate and 57% probability of observing at least 1 DLT with 10% incidence rate.

10.2 Analysis Sets, and Covariates

10.2.1 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 160 or pembrolizumab.

The analysis of DLT will be conducted on the DLT Analysis Set defined as all subjects from the Safety Analysis Set with an evaluable DLT endpoint. The DLT endpoint is

evaluable if either: 1) the subject experiences a DLT, or 2) the subject does not experience a DLT and completes cycle 1 of treatment as planned.

10.2.2 Covariates

Not applicable

[redacted]

10.2.4 Handling of Missing and Incomplete Data

The handling of missing and incomplete data is described in the statistical analysis plan.

10.3 Adaptive Design

For Part 1 (AMG 160 Monotherapy), a 2-parameter BLRM (Neuenschwander et al, 2008) is used to guide dose exploration. The design seeks to identify the MTD or RP2D, which is defined as a dose most likely to have a DLT rate in the target toxicity probability interval (TPI), but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). In this study, the target TPI is defined as (0.20, 0.33] and excessive and unacceptable TPIs are defined as (0.33, 0.60] and (0.60, 1.00], respectively, with an overdose control limit of less than 0.40 probability of excessive or unacceptable TPI. The probability of a DLT at dose level di is assumed to follow a Bernoulli distribution with probability pi where the logit of pi increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

$$\log [pi / (1\text{-}pi)] = \text{logit}(pi) = \log[a] + \exp(\log[b]) \log (di / dref)$$

where a and b are random variables and dref is 1 of the planned dose selected as the reference dose.

A bi-variate normal prior distribution was selected for theta = (log a, log b). The mean/standard deviation for “log a” were selected as -1.099/1.122 and for “log b” as -1.243/1.981 with a correlation of 0. These values were selected such that pi is 0.05 for the initial planned dose (0.003 mg) and 0.25 for the reference dose ([redacted] mg), where the probability that the true DLT rate is $\leq$ 0.40 at the lowest dose is 0.90 and the probability the true DLT rate is $\leq$ 0.05 at the reference dose is 0.05.

Operating characteristics of this design are described in Section 12.8.

The dose expansion stopping rules described in Section 7.4.1.2 are derived using a Bayesian approach developed in 1995 by Thall et al, 1995. The prior distribution describing the event rate is a Beta (0.40, 1.60) distribution. The threshold for terminating the study is a posterior probability > 80% for an event rate greater than 20%.

In Part 2 (AMG 160 Combination with Pembrolizumab), dose escalation decisions will be guided by the modified toxicity probability interval design (mTPI-2). See Section 12.16 for additional information.

10.4 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. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

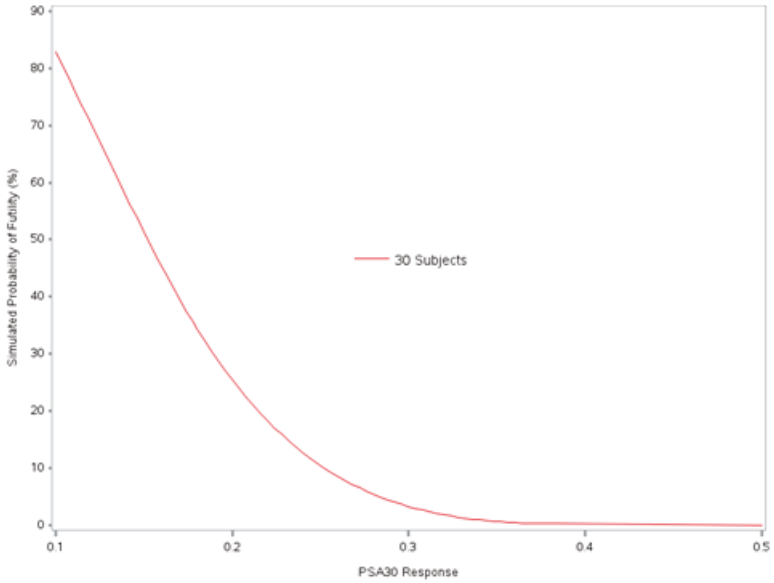
10.4.1 Planned Analyses

10.4.1.1 Interim Analysis and Early Stopping Guidelines

Safety data will be reviewed on an ongoing basis. For Part 1 (AMG 160 Monotherapy), accumulating toxicity information BLRM will be used to make dosing recommendations. In DLRMs, Amgen, in consultation with the site investigators, will review the BLRM recommended dose level and will review all available cumulative data by cohort prior to making dose escalation recommendations. As a sensitivity analysis, a 1-parameter Continual Reassessment Method model may be used to estimate the dose-toxicity relationship to help making dose escalation decisions. Adverse events and DLTs observed in all subjects will be evaluated continually and fully integrated into all DLRMs and considered in all enrollment and dosing decisions.

The futility analysis of PSA30 will be performed when the first 30 evaluable subjects reach cycle 3 day 1 for subjects in Part 1 dose expansion. If the posterior probability of PSA30 response < 18% is > 70% for the first 30 evaluable subjects, the cohort will be declared futile. Equivalently, if < 5 PSA30 responders are observed in a cohort, the cohort will be declared futile. The posterior probability is calculated based on a noninformative prior distribution Beta (0.5, 0.5). The probability of stopping at futility if PSA30 ≤ 18% is approximately 35% (see Figure 10-1).

Figure 10-1. The Probability of Stopping at Futility



In Part 2 (AMG 160 Combination with Pembrolizumab), dosing recommendations will be guided by the modified toxicity probability interval design (mTPI-2). See Section 12.16 for additional information.

A formal interim analysis of available safety and efficacy data will occur when all remaining dose-escalation subjects have had the opportunity to complete 28 days on study for Part 1. A similar interim analysis will be conducted for Part 2 when all remaining subjects have had the opportunity to complete 28 days on the study. This interim analysis will estimate the MTD (MTD1, MTD2, MTD3, and/or MTD4, as applicable if step-dosing is implemented), support the determination of the RP2D, and support the evaluation of benefit/risk profile of AMG 160 as monotherapy and in combination with pembrolizumab.

[redacted]

An interim analysis will not be performed for Part 3 and Part 6 (will be part of the final analysis).

[redacted]

10.4.1.2 Primary Analysis

The primary analysis will only include Part 1 dose exploration [redacted] and Part 1 dose-expansion cohort 1a, other parts will be analyzed as part of the final analysis.

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

10.4.1.3 Final Analysis

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

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

Descriptive statistics will be provided for selected demographics, safety, pharmacodynamic [redacted] data by treatment (monotherapy vs combination with pembrolizumab), dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	Listings of secondary efficacy endpoints will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts. For all subjects treated at the MTD and/or RP2D, the proportion of subjects with an objective response per RECIST 1.1 along with corresponding exact 95% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934); similarly, the proportion of subjects and 95% CI will be tabulated for PSA response, ^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT based response, 1-year OS, 2-year OS, 3-year OS, circulating tumor cells response and CTC response/conversion. Kaplan Meier curve will be presented for duration of response, time to progression (radiographic and PSA), progression-free survival (radiographic and PSA), OS with estimates for rates, and other PCWG3-recommended endpoints (time to symptomatic skeletal events, alkaline phosphatase [total, bone], LDH, hemoglobin, neutrophil-to-lymphocyte ratio, urine N-telopeptide), and 95% CI at selected weeks if data allows.
Exploratory	Will be described in the supplemental statistical analysis plan finalized before database lock.

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint(s)

Endpoint	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 160 or pembrlizumab. Subject incidence of DLT will be tabulated by planned dose level. A table of DLT will be provided. The probability of a subject having a DLT by dose level will be estimated using a two-parameter BLRM model (Part 1). The statistical analysis methods for other safety endpoints are described in Sections 10.4.2.3.2 through 10.4.2.3.6.

10.4.2.3.2 Adverse Events and Disease-related Events

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

10.4.2.3.3 Laboratory Test Results

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

10.4.2.3.4 Vital Signs

Vital signs data will be reviewed for each subject. The analyses of vital signs will include summary statistics over time and/or changes from baseline over time may be provided.

10.4.2.3.5 Physical Measurements

Physical measurements will be reviewed for each subject.

10.4.2.3.6 Electrocardiogram

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters. Subjects' maximum change from baseline in QTcF will be categorized and the number and percentage of subjects in each group will be summarized. Subjects' maximum post baseline values will also be categorized and the number and percentage

of subjects in each group will be summarized. All on-study ECG data will be listed and select parameters of interest plotted.

[redacted]

10.4.2.3.8 Exposure to Investigational Product

Details of AMG 160 administration will be listed for every subject.

10.4.2.3.9 Exposure to Concomitant Medication

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

10.4.2.4 Other Analyses

For AMG 160, pharmacokinetic parameters will be determined from the time concentration profile using standard non-compartmental approaches and considering the profile over the complete sampling interval.

[redacted]

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
[redacted]	
ADT	androgen-deprivation therapy
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ALP	alkaline phosphatase
[redacted]	
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
BIL	bilirubin
BiTE	bispecific T-cell engager
BLRM	Bayesian logistic regression model
[redacted]	
CAR-T	chimeric antigen receptor T-cell
CD	cluster of differentiation
CFR	US Code of Federal Regulations
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete response
CRF	case report form
CRS	cytokine release syndrome
CT	computed tomography
CTC(s)	circulating tumor cell(s)
CTC0	CTC-response
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	
CYP	cytochrome P450
DILI	drug-induced liver injury
DLRM	Dose Level Review Team Meeting
DLRT	Dose Level Review Team
DLT	dose-limiting toxicities
DOR	duration of response
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECHO	echocardiogram

Abbreviation or Term	Definition/Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDC	electronic data capture
eIV	extended intravenous
EMA	European Medicines Agency
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
EOI	end of infusion
EU	European Union
Fc	fragment crystallizable
FDA	Food and Drug Administration
FDG PET/CT	fluorodeoxyglucose PET/CT
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
HLA	human leukocyte antigen
HLE	half-life extended
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
INR	international normalized ratio
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IV	intravenous
IVSS	intravenous solution stabilizer
JAK	janus kinase
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone agonist
LTFU	long-term follow-up

Abbreviation or Term	Definition/Explanation
MABEL	minimum anticipated biological effect
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA scan	multigated acquisition scan
NCT	National Clinical Trials
OR	objective response
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamics
PDE4	phosphodiesterase-4
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	orally
PR	partial response
PSA	prostate-specific antigen
PSMA	prostate specific membrane antigen
Q2W	every 2 weeks
[redacted]	
QD	once daily
RP2D	recommended phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	
scFc	single chain fragment crystallizable
SFU	safety follow-up
Source Data	information from an original record or certified copy of the original record containing subject information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that AMG 160 or pembrolizumab is/are administered to the subject
TBL	total bilirubin
TLS	tumor lysis syndrome
TNFα	tumor necrosis factor alpha
TPI	toxicity probability interval

Abbreviation or Term	Definition/Explanation
ULN	upper limit of normal
US	United States
USPSTF	US Preventive Services Task Force
WFI	water for injection

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 and Table 12-2 will be performed by the central laboratory and/or by the local laboratory. 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 6.1 to 6.2 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 12-1. LOCAL Laboratory Analyte Listing

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	APTT	Specific gravity	RBC	Testosterone
Potassium	PT/INR	pH	Hemoglobin	PSA
Chloride	Fibrinogen	Blood	Hematocrit	
Bicarbonate	D-dimer	Protein	Reticulocytes	
Total protein		Glucose	Platelets	
Albumin		Bilirubin	WBC	
Calcium		WBC	Differential	
Adjusted calcium		RBC	• Neutrophils	
Magnesium		Epithelial cells	• Eosinophils	
Phosphorus		Bacteria	• Basophils	
Glucose		Casts	• Lymphocytes	
BUN or Urea		Crystals	• Monocytes	
Creatinine			ANC	
Uric acid				
Total bilirubin				
Direct bilirubin				
AST (SGOT)				
ALT (SGPT)				
ALP				
LDH				
CRP				
Ferritin				
GFR[a]				

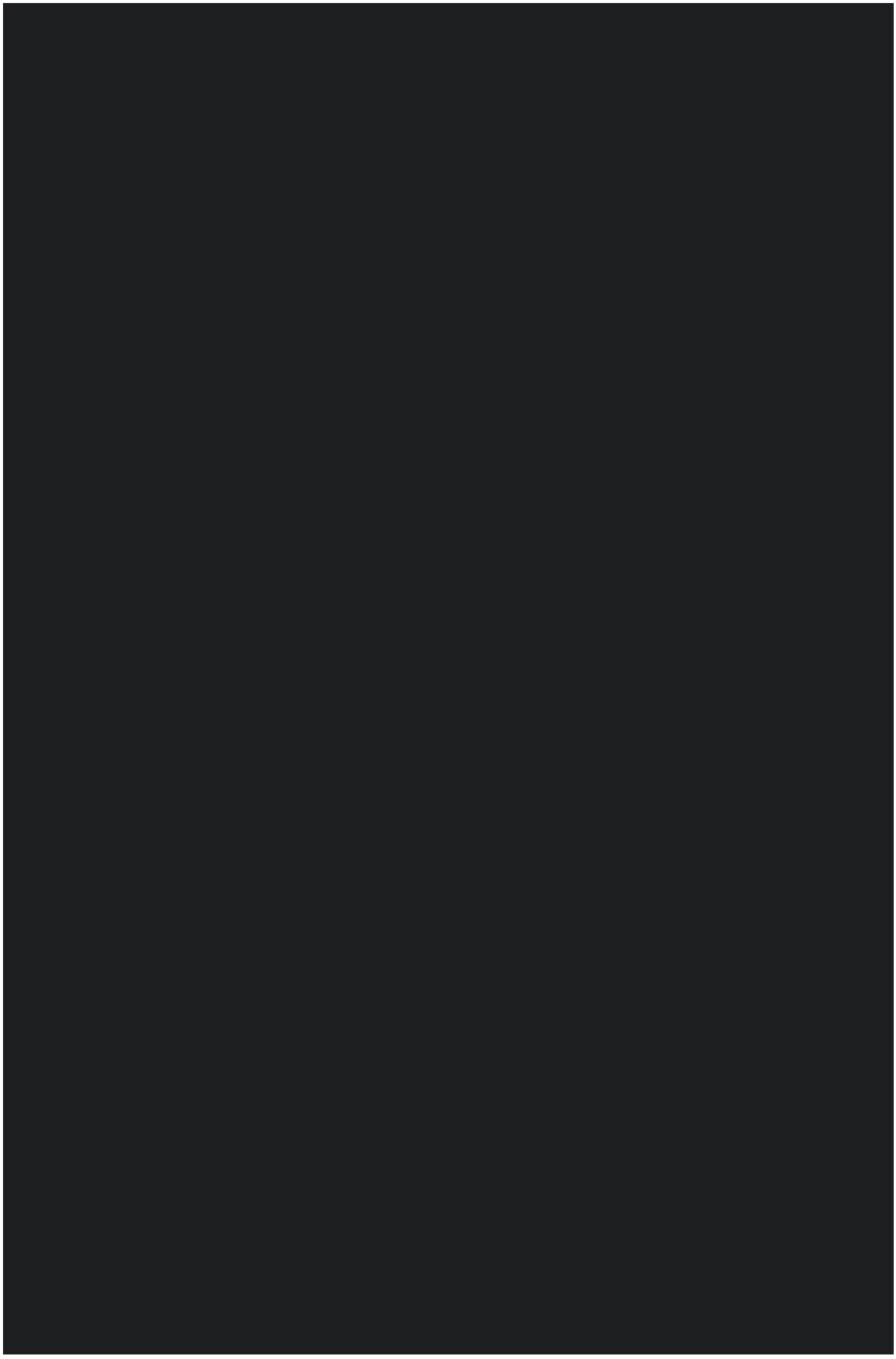
ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell count; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; WBC = white blood cell count

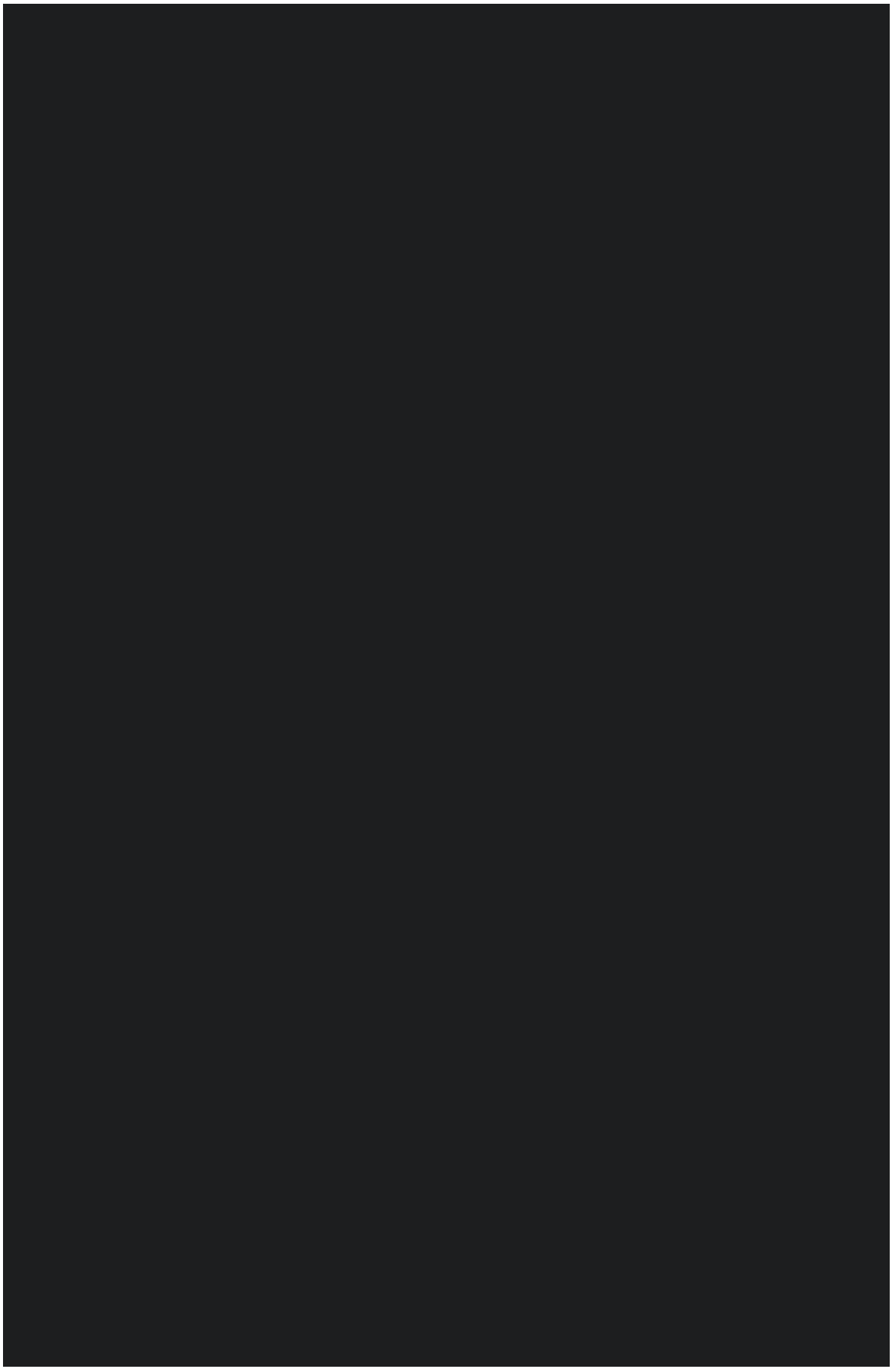
[a] Creatinine clearance will be calculated using the Cockcroft-Gault equation:
(140 - age [years] x weight [kg] x 0.85 if female) / (72 x creatinine mg/dL), adjusted for BSA by 1.73 m2/BSA

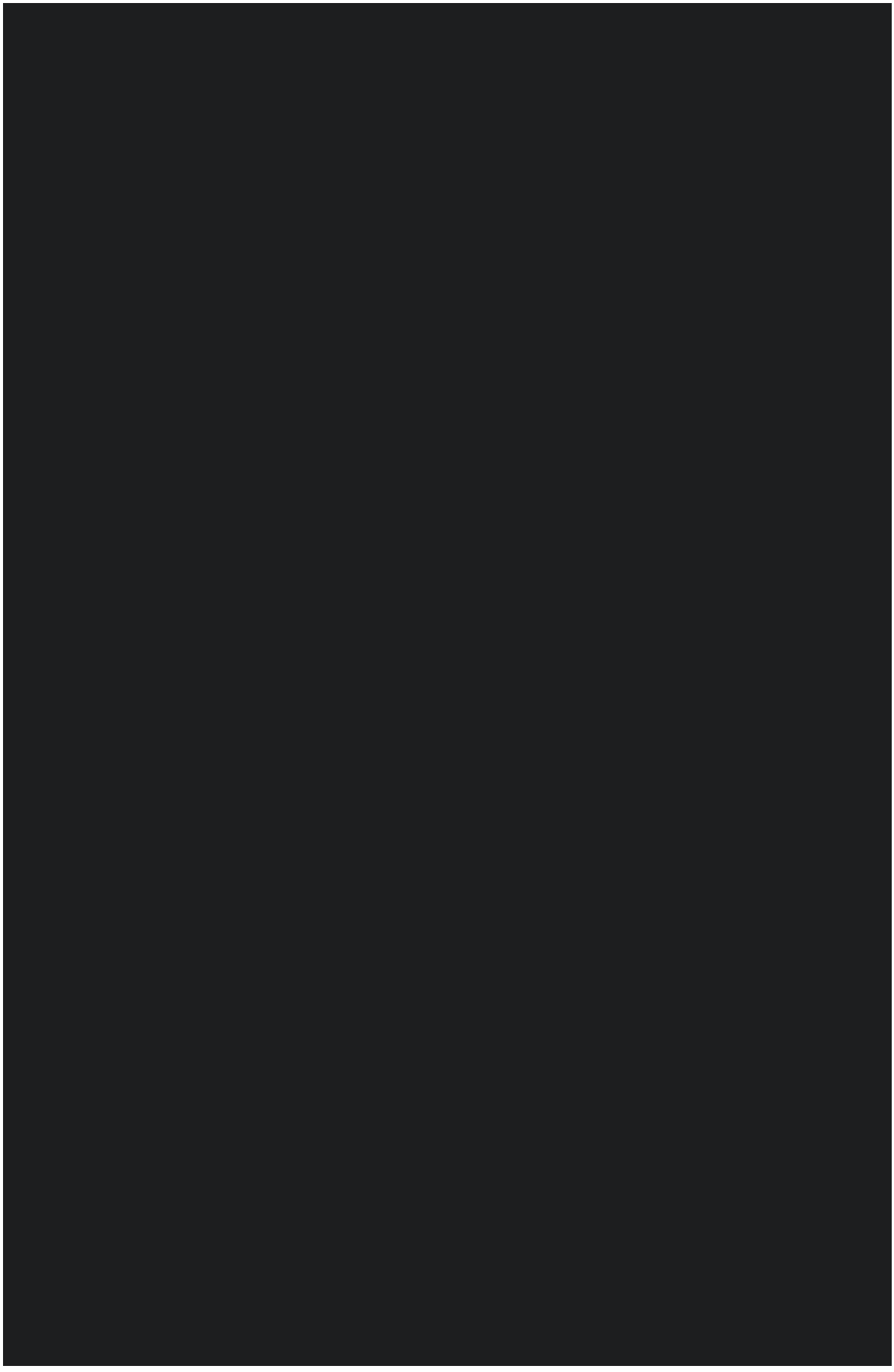
Table 12-2. CENTRAL Laboratory Analyte Listing

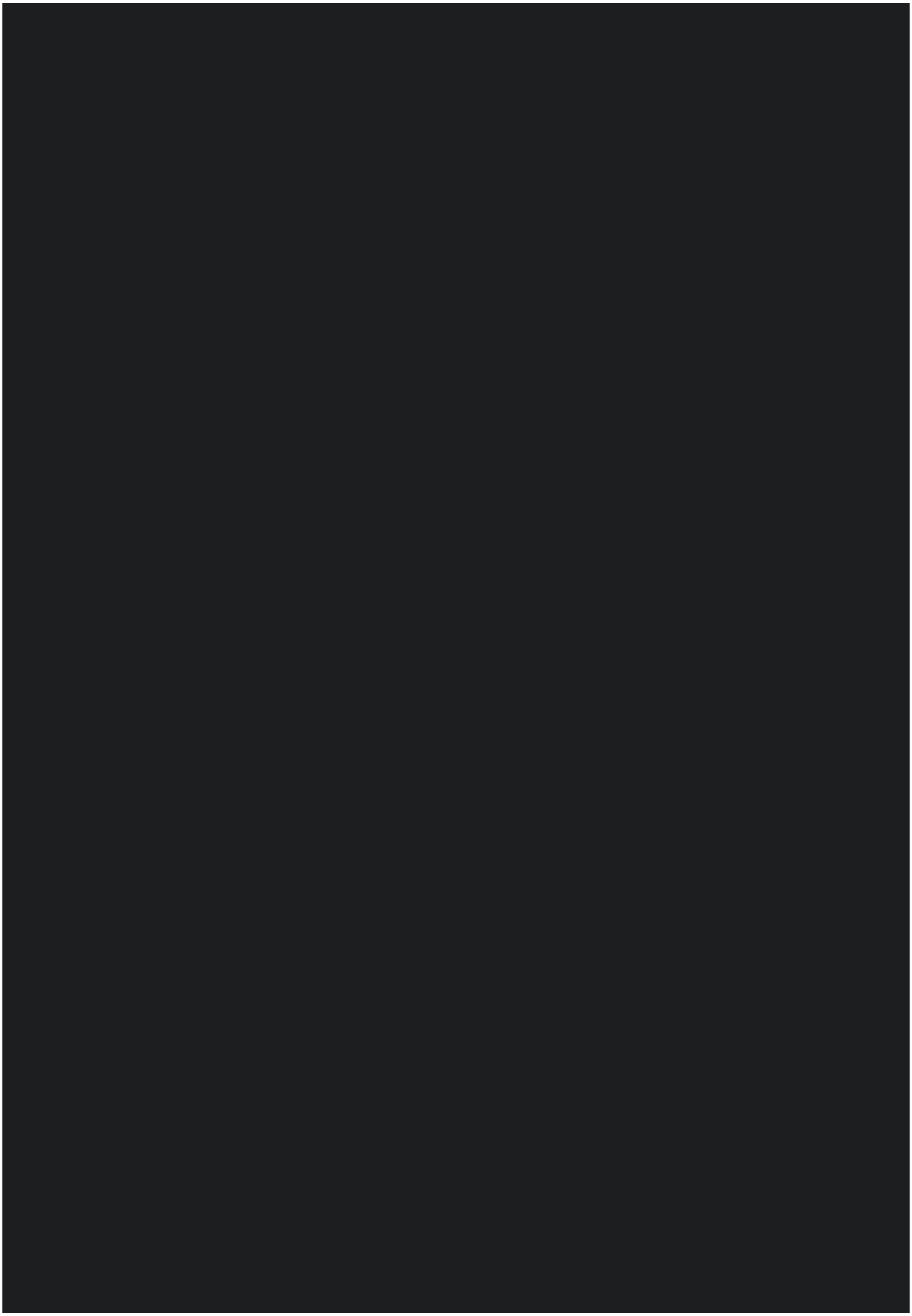
[redacted]
• AMG 160 PK • PSA (total and free)
[redacted]
• ALP (total and bone) • urine N-telopeptide • LDH
[redacted]

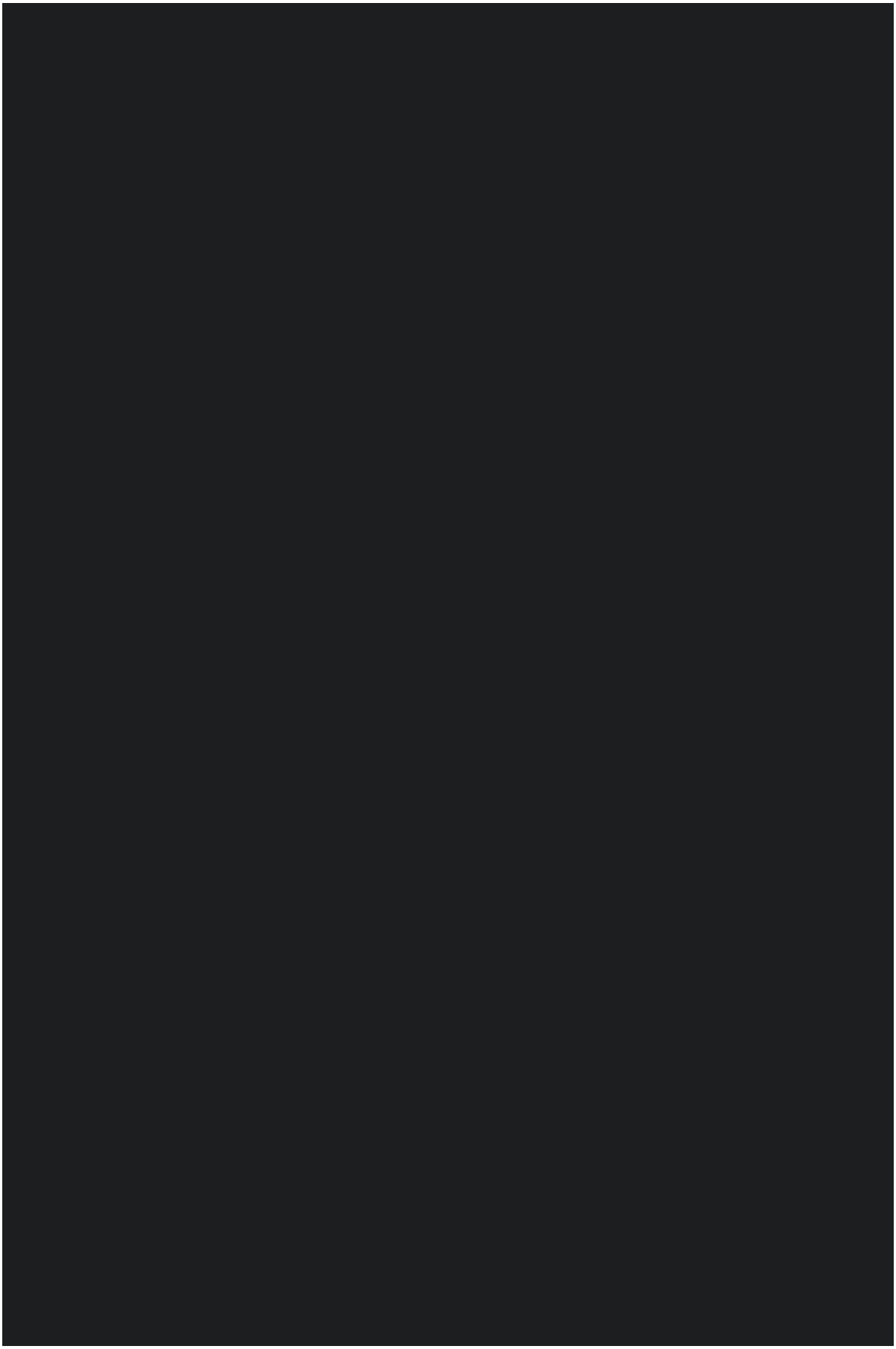
ALP = alkaline phosphatase; [redacted] leukocyte antigen; LDH = lactate dehydrogenase; [redacted] PK = pharmacokinetics; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

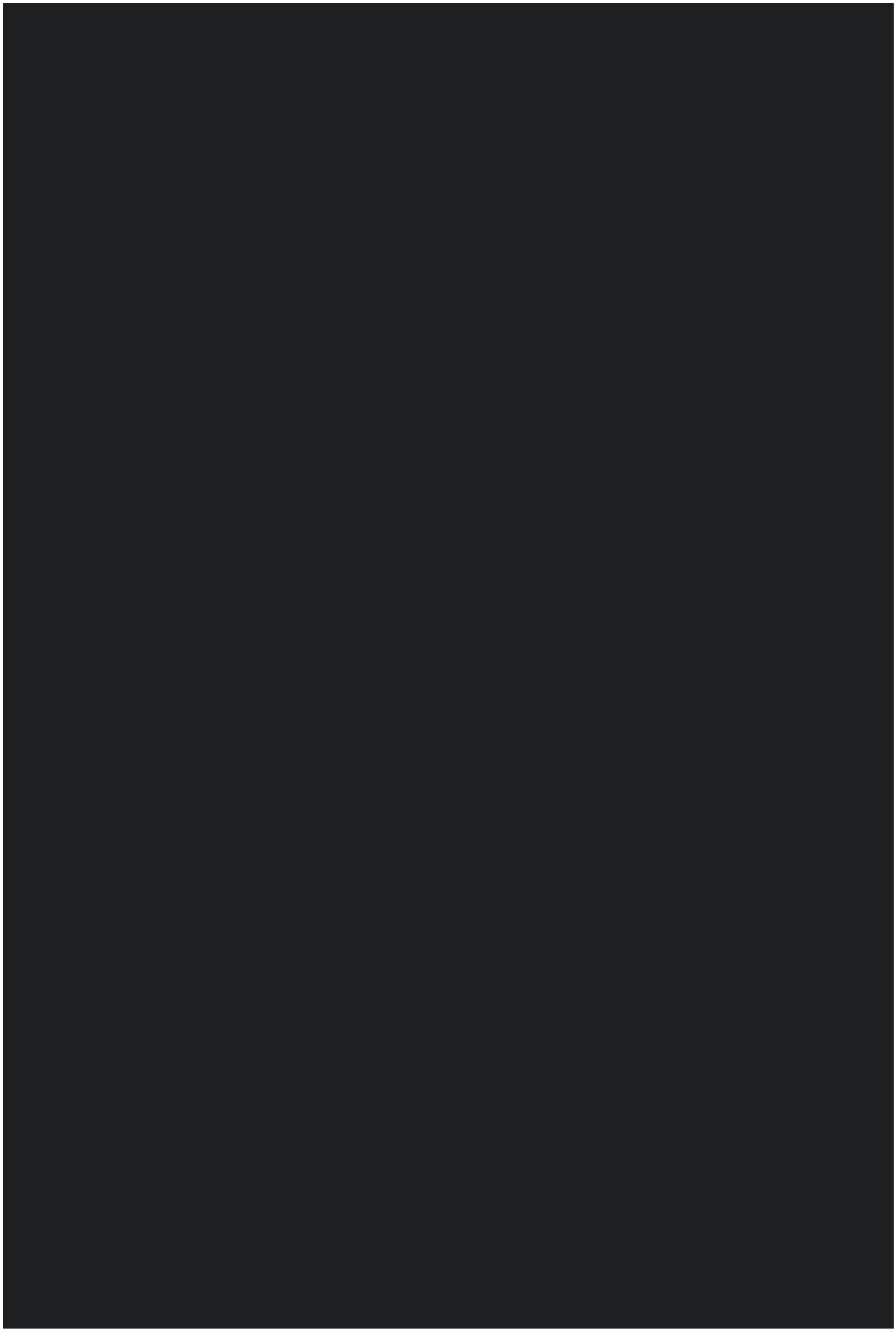


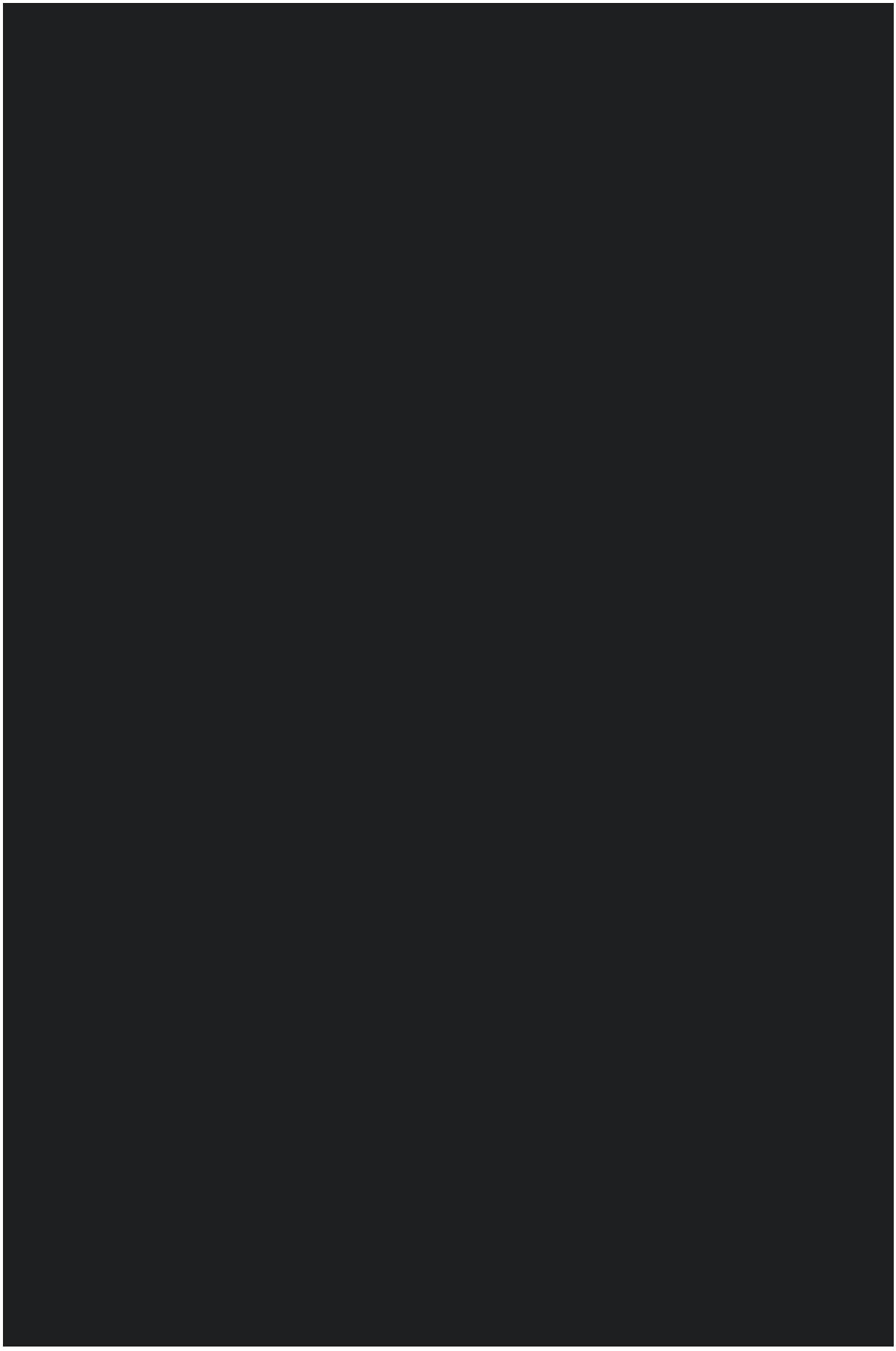


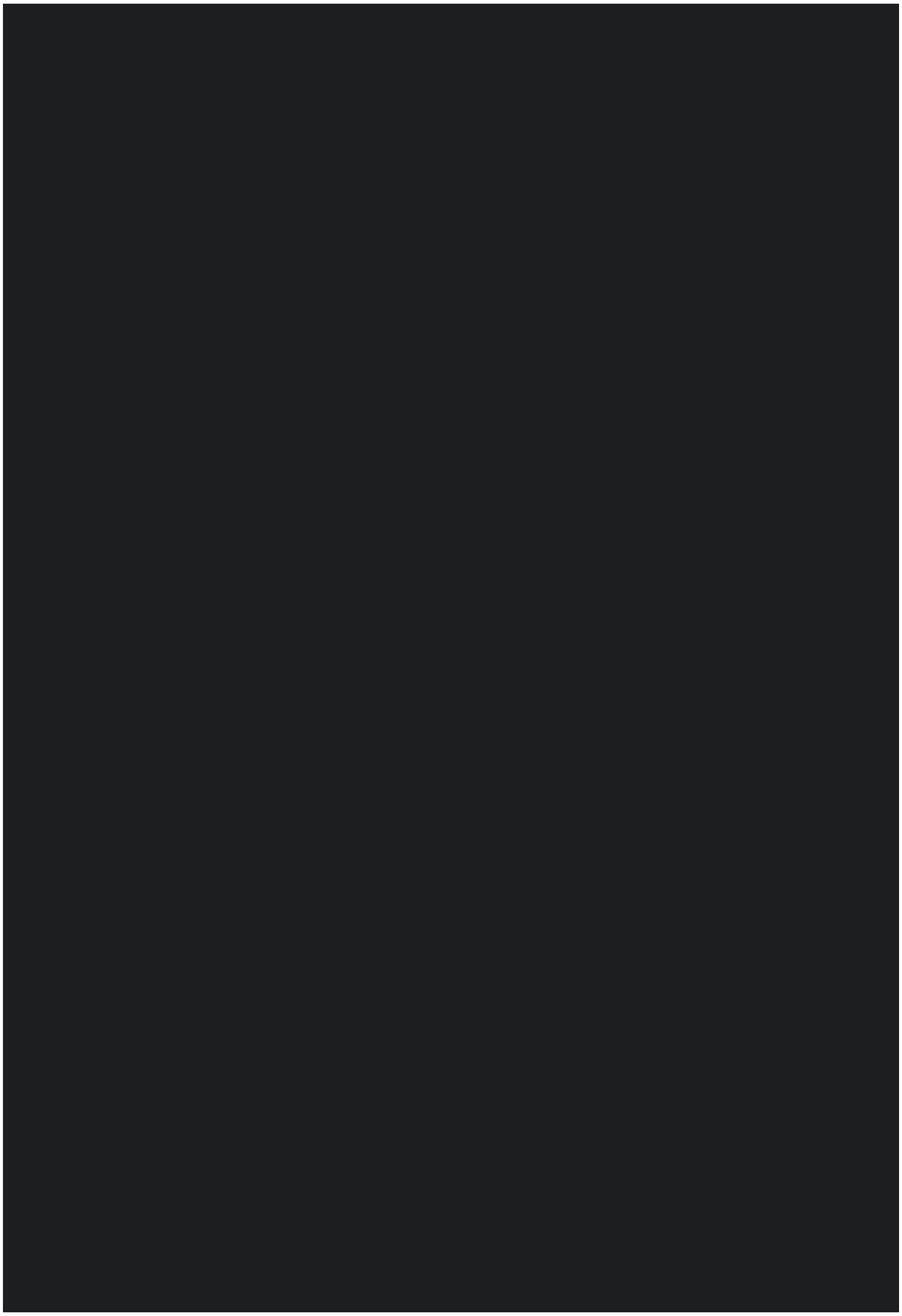














12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition
• Disease-related events are events anticipated to occur in the study population due to the underlying disease. See Section 12.11 for the list of disease-related events. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. • Disease-related events that would qualify as an adverse event or serious adverse event: – An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event. • Disease-related events that do not qualify as adverse events: – An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

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 SAP.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [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 pre-existing 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. In addition, a dose of $>$ 10% higher than the intended AMG 160 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event." • For situations when an adverse event or serious adverse event is due to metastatic castration-resistant prostate cancer (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 prostate cancer). Note: The term "disease progression" should not be used to describe the disease related event or 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 pre-existing 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 pre-existing 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.

[redacted]

[redacted]

Recording Adverse Events, Disease-related Events (if applicable), Serious Adverse Events, and Serious Disease-related Events (if applicable)

Adverse Event, Disease-related Event (if applicable), Serious Adverse Event Recording, and Serious Disease-related Events (if applicable)
• When an adverse event, disease-related 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/disease-related event/serious adverse event information in the Event case report form (CRF). – Additionally, the investigator is required to report a fatal disease-related event on the Events CRF. • The investigator must assign the following adverse event attributes: – adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – dates of onset and resolution (if resolved); – 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, non-Amgen wearable devices, and/or study-mandated procedures including ^{68}Ga-PSMA-11; – action taken; and – outcome of event. • If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Events CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to Amgen 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, version 5.0 which is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

with the exception of cytokine release syndrome (CRS), which must be graded using the criteria referenced in the publication by Lee et al (2014) (see Section 12.12) and tumor lysis syndrome (TLS), which must be graded according to the Cairo Bishop criteria referenced in the publication by Coiffier et al (2008) (see Section 12.13), and immune-effector cell associated neurologic syndrome (ICANS) will be using the criteria referenced in the publication by Lee et al (2019) (see Section 12.14).

Assessment of Causality

- The investigator is obligated to assess the relationship between investigational product(s), protocol-required therapies, non-Amgen wearable devices, and/or study-mandated procedures, including ^{68}Ga-PSMA-11, and each occurrence of each adverse event/serious adverse event.
- 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 as defined in Section 9.1, the investigator will provide Amgen with a copy of any post-mortem 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 within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 12-1). • 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 Contingency Report Form to report the event.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

A
Study # 20180101
AMG 160

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator				Country

Reporter	Phone Number				Fax Number
	( )				( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

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

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP?												Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						AMG 160		^{68}GA-PSMA-11		^{18}F-FDG		^{18}F-DCFPyL		etanercept		Pembrolizumab			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No ✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No															
				☐Yes ☐No															
				☐Yes ☐No															

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

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*
Page 1 of 3

A Study # 20180101 AMG 160	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

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

Date Admitted Day Month Year				Date Discharged Day Month Year

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

			Prior to, or at time of Event					Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld			Lot # and Serial #
IP/Amgen Device:		Date of Initial Dose Day Month Year	Date of Dose Day Month Year	Dose	Route	Frequency					
AMG 160	☐blinded ☒ open label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
etanercept	☐blinded ☒ open label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
^{68}GA-PSMA-11	☐blinded ☒ open label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
^{18}F-FDG	☐blinded ☒ open label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
^{18}F-DCFPyL	☐blinded ☒ open label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Pembrolizumab	☐blinded ☒ open label										Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

FORM-056006 *Version 7.0 Effective Date: 1 February 2016*
Page 2 of 3

A Study # 20180101 AMG 160	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date (Day Month Year)	Test											
	Unit											

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

Date (Day Month Year)	Additional Tests	Results	Units

A Study # 20180101 AMG 160	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

A Study # 20180101 AMG 160	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy Information

Study-specific contraception requirements for male subjects are outlined in Section 6.2.

Male subjects must receive pregnancy prevention counseling and be advised of the risk to the fetus if they father a child during treatment and for 6 months after the last dose of AMG 160 monotherapy or in combination with pembrolizumab.

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 AMG 160 monotherapy or in combination with pembrolizumab

The female partner should consider using an acceptable method of effective contraception such as: hormonal, intrauterine device, intrauterine hormonal-releasing system, female barrier method (diaphragm, cap, sponge [a female condom is not an option 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 (defined below) or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- premenopausal female with 1 of the following:
  - documented hysterectomy;
  - documented bilateral salpingectomy; or
  - documented bilateral oophorectomy.

    Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- premenarchal female

- postmenopausal female:
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Unacceptable Methods of Birth Control for Male Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

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 AMG 160 monotherapy or in combination with pembrolizumab, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization 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 authorization 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 12-2. 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: _20180101_____

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 160				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

12.6 Appendix 6. Sample Storage and Destruction

Any blood, tumor, biomarker, or pharmacokinetics (PK) samples collected according to the Schedule of Activities (Section 2.2) 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 prostate cancer, the dose response and/or prediction of response to AMG 160, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining 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 12.3 for subject confidentiality.

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

Subjects with abnormal hepatic laboratory values (ie, 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 (BIL) glucuronidation (eg, indinavir, atazanavir)
- alpha-one 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 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) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-3. 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 absence of CRS and without other alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)

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 AMG 160 is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-3) 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 within 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 12.4.

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 12-3 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, 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 (LDH), and peripheral blood smear
- appropriate liver imaging if clinically indicated
- appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, and 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.

12.8 Appendix 8. Operating Characteristic for 2-parameter BLRM Design

The operating characteristics of the two-parameter Bayesian logistic regression model (BLRM) design were evaluated via simulation using EAST software version 6.4. The cohort size was fixed to 3 or 4 subjects. Planned dose levels were assigned as 0.003, 0.01, 0.03, 0.09, 0.15, 0.3, 0.6, 0.9, [redacted]mg. After simulated enrollment of the initial cohort at the initial dose level, simulations selected the subsequent dose levels based on the following rules:

- After each cohort, the next dose was the one with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.40 probability of an excessive or unacceptable TPI.
- Skipping a planned dose level was not allowed.

Dose exploration was stopped when either of the following occurred:

- The model recommended a dose level where at least 6 subjects had already received treatment at this recommended level.
- A maximum number of 50 subjects were treated.

Operating characteristics are described below.

Operating characteristics

The design was evaluated for 4 possible dose-response scenarios: “Low”, “Mid”, and “High” maximum tolerated dose (MTD) and an “Extreme” scenario where every planned dose level was excessively toxic. Table 12-4 shows the dose level and true probability of dose-limiting toxicity (DLT) for each scenario used in the simulated studies. Since the timing of initiation of the multiple subject cohorts impacts the design operating characteristics, the operating characteristics were calculated separately for each possible timing for starting the multiple subject cohorts: at cohort 1, cohort 2, cohort 3, cohort 4 and at cohort 5. Overall operating characteristics are reported after weighting the 5 timing-specific operating characteristics by the probability that a specific cohort is the initial multiple subject cohort. Table 12-5 shows the dose level and true probability of a DLT or a grade 2 related adverse event for each scenario used in the simulated studies. Using the toxicity rates described in Table 12-5, the probability by cohort for initiating the multiple subjects cohorts are shown in Table 12-6. Table 12-7 reports the operating characteristics from 1000 simulated studies estimating the MTD when the target TPI is (0.20, 0.33]. The rate of MTD selected and the average number of subjects assigned to each dose level are presented in Table 12-8.

Table 12-4. True Probability of DLT by Scenario

Dose level (mg)	0.003	0.01	0.03	0.09	0.3	0.9	[redacted]
MTD Scenario							
High	0.01	0.04	0.08	0.10	0.12	0.15	
Mid	0.08	0.10	0.12	0.15	0.20	0.30	
Low	0.12	0.15	0.20	0.30	0.40	0.50	
Extreme	0.35	0.40	0.45	0.55	0.60	0.65	

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

Table 12-5. True Probability of DLT or Grade 2 Related Adverse Event by Scenario

Dose level (mg)	0.003	0.01	0.03	0.09	0.3	0.9	[redacted]
MTD Scenario							
High	0.06	0.09	0.13	0.15	0.17	0.25	
Mid	0.13	0.15	0.17	0.25	0.30	0.40	
Low	0.17	0.25	0.30	0.40	0.50	0.60	
Extreme	0.45	0.50	0.55	0.65	0.70	0.75	

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

Table 12-6. Probability by Planned Dose Level for Initiating Multiple Subject Cohorts by Scenario

Planned dose level (mg) for initiating multiple subject cohorts	0.003	0.01	0.03	0.09	[redacted]
MTD Scenario					
High	0.06	0.08	0.11	0.11	
Mid	0.13	0.13	0.13	0.15	
Low	0.17	0.21	0.19	0.17	
Extreme	0.45	0.27	0.15	0.08	

MTD = maximum tolerated dose

Table 12-7. Operating Characteristics by Scenario

MTD scenario	High		Mid		Low		Extreme	
Number of subjects per cohort	4	3	4	3	4	3	4	3
Average number of subjects on study	23.1	19.5	21.3	18.2	17.7	15.2	8.9	7.8
Average number of DLTs on study	3.0	2.4	3.9	3.3	4.4	3.8	3.4	2.9
Percentage of studies recommending dose with DLT probability of (%):								
$< 10\%$	5.7	6.1	13.0	14.1	39.6	38.2	88.9*	87.4*
$\geq 10\%$ and $< 20\%$	44.3	41.7	9.6	11.0	3.3	3.3	0.0	0.0
$\geq 20\%$ and $< 33\%$	45	47.1	67.9	64.5	33	32.4	0.0	0.0
$\geq 33\%$	3.8	3.9	9.3	10.4	23.8	26.1	9.9	11.7
$\geq 15\%$ and $\leq 33\%$	73.2	75	75.5	73.4	35.6	35.1	0.0	0.0

DLT = dose-limiting toxicity; MTD = maximum tolerated dose
* Represents the percentage of studies in extreme scenario where MTD is determined to be below the lowest planned dose level of 0.003 mg

Table 12-8. The Rate of MTD Selected and the Number of Subjects Assigned at Each Dose Level by Scenario

MTD Scenario	High		Mid		Low		Extreme	
Number of Subjects Per Cohort	4	3	4	3	4	3	4	3
Rate of maximum tolerated dose selected at each dose level (%):								
Below lowest dose	5.4	5.8	12.9	14.0	39.6	38.2	88.9	87.4
0.003 mg	<0.01	0.00	0.11	0.18	0.71	0.67	2.2	2.7
0.01 mg	0.04	0.03	0.43	0.50	2.6	2.7	2.8	2.8
0.03 mg	0.26	0.32	1.6	1.6	9.7	9.9	3.1	3.7
0.09 mg	1.5	2.0	7.6	8.9	23.3	22.5	1.5	2.1
0.3 mg	14.6	11.8	36.8	31.4	20.7	20.9	0.36	0.33
0.9 mg	28.2	27.9	31.1	33.1	2.9	4.9	0.00	0.04
[redacted]								
Average number of subjects at each dose level								
0.003 mg	0.30	0.28	0.73	0.64	1.2	1.1	2.4	2.2
0.01 mg	0.69	0.62	1.4	1.1	2.2	1.9	2.5	1.9
0.03 mg	1.2	1.2	2.1	1.7	3.2	2.6	1.8	1.5
0.09 mg	1.9	1.8	3.0	2.9	4.1	3.2	0.93	0.89
0.3 mg	5.2	3.6	5.6	4.2	3.8	3.0	0.32	0.30
0.9 mg	4.9	3.9	4.1	3.6	0.94	1.1	0.01	0.03
[redacted]								

MTD = maximum tolerated dose

12.9 Appendix 9. Performance Status According to Eastern Cooperative Oncology Group (ECOG) Scale

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

ECOG = Eastern Cooperative Oncology Group.
Source: Oken et al, 1982

12.10 Appendix 10. 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 contrast, a cross-sectional magnetic resonance imaging (MRI) scan of the abdomen and pelvis, with a noncontrast CT scan of the chest, may be considered. In phase I and II 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 nonmeasurable/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 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. 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 end point 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, 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.

12.11 Appendix 11. Expected Disease-related Events for Metastatic Castration-resistant Prostate Cancer

System Organ Class	Disease-related Adverse Events
Blood and Lymphatic system disorders	Anemia, neutropenia, leukopenia, thrombocytopenia
Investigations	Hemoglobin decreased, platelet count decreased, white blood cell count decreased, calcium increased
Metabolism and nutrition disorders	Hypercalcemia
Musculoskeletal and connective tissue disorders	Skeletal pain, bone pain, pathological fractures, bone pain, pain in extremity,
Nervous system disorders	Spinal cord compression
Renal and urinary disorders	Incontinence, urge incontinence, urinary incontinence, urinary retention, urinary straining, urinary flow decreased, hematuria
Reproductive system and breast disorders	Prostate induration, prostate tenderness, prostatic asymmetry, prostatic hemorrhage, prostatic mass, prostatic obstruction, prostatomegally, erectile dysfunction

12.12 Appendix 12. 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 infusion of AMG 160 monotherapy or in combination with pembrolizumab. CRS may be life threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of CRS. Throughout the treatment with AMG 160, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to CRS.

Grading and management of CRS should be performed according to the guidelines provided in Table 7-9 (based on the adopted grading system referenced in Lee et al, 2014).

Please also refer to the general guidance for re-start of infusion after interruptions/delay/withholding and dose modifications in Section 7.4.2.4.

For grade 3 and 4 CRS, please also see Section 7.4.1.3 for dose-limiting toxicity (DLT) considerations.

Fever reported outside the context of CRS will be graded per CTCAE version 5.

12.13 Appendix 13. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 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 4.0. Cairo and Bishop developed a system for defining and grading TLS based on Hande-Garrow classification of laboratory or clinical TLS (Coiffier et al, 2008). For this trial, the Cairo-Bishop classification will be used to define presence of TLS, ie, presence of laboratory TLS (see Table 12-9) and clinical TLS (see Table 12-10) 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 12-9).

Table 12-9. 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 (Table 12-10). The grade of clinical TLS is defined by the maximal grade of the clinical manifestations as detailed in Table 12-10.

Table 12-10. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

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

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

12.14 Appendix 14. Specific Guidance for Immune-effector Cell-associated Neurologic Syndrome

For this trial, immune-effector cell associated neurologic syndrome (ICANS) will be using the criteria referenced in the publication by Lee et al (2019). While the grading system has been developed in large part from chimeric antigen receptor T-cell (CAR-T) therapies, symptoms of ICANS may be shared among immune effector-cell associated therapies such as bispecific T-cell engager (BiTE) molecules. Although there may be a wide range of symptoms associated with ICANS, subjects may have a stereotypic course of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy.

ICANS grade is determined by the most severe event (eg, depressed level of consciousness, seizure, motor findings, raised intracranial pressure [ICP]/cerebral edema) not attributable to any other cause. Refer to the ICE score below for grading of ICANS.

Immune Effector Cell-associated Encephalopathy (ICE) Assessment Tool

- Orientation: Orientation to year, month, city, hospital: 4 points
- Naming: ability to name 3 objects (eg, point to clock, pen, button): 3 points
- Following commands: ability to follow simple commands (eg, “Show me two 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
- Attention: ability to count backwards from 100 by 10: 1 point

ICE scoring

- 7-9, grade 1
- 3-6, grade 2
- 0-2, grade 3
- 0 due to subject unarousable and unable to perform ICE
- Assessment, grade 4

Table 12-11. ASBMT Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS) Consensus Grading for Adults

Neurotoxicity Domain[a]	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[b]	7-9	3-6	0-2	0 (subject is unarousable and unable and unable to perform ICE)
Depression level of consiousness[c]	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	N/A	N/A	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	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ASBMT = American Society for Blood and Marrow Transplantation; CTCAE = Common Terminology Criteria for Adverse Events; EEG = electroencephalogram; ICANS = immune-effector cell associated neurologic syndrome; ICE = immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable.

[a] Other signs and symptoms such as headache, tremor, myoclonus, asterixis, and hallucinations may occur and could be attributable to immune effector-cell engaging therapies. Although they are not included in this grading scale, careful attention and directed therapy may be warranted.

[b] 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.

[c] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[d] Intracranial haemorrhage 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

Assessment and Supportive Care Recommendations (all grades)

- Neurologic assessment and grading at least twice a day to include cognitive assessment and motor weakness
- Magnetic resonance imaging of the brain with and without contrast (or brain computed tomography [CT] if MRI is not feasible) for ≥ grade 2 neurotoxicity
- Neurology consultation at first sign of neurotoxicity

- Conduct electroencephalogram (EEG) for seizure activity for ≥ grade 2 neurotoxicity
- Aspiration precautions; intravenous (IV) hydration
- Use caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)

Table 12-12. Assessment and Supportive Care Recommendations

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS
Grade 1	• Supportive care	In the setting of grade ≥ 3 CRS with hypotension, tocilizumab[e,f] 8 mg/kg IV over 1 h (not to exceed 800 mg/dose)[d]
Grade 2[c]	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen.	Anti-IL-6 therapy as per grade 1[d] Consider transferring subject to ICU if neurotoxicity associated with grade ≥ 2 CRS
Grade 3[c]	• Supportive care • Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h[a] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if subject had persistent grade ≥ 3 neurotoxicity.	Anti-IL-6 therapy as per grade 1[d]
Grade 4[c]	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids [a,b] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if subject has persistent grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.	Anti-IL-6 therapy as per grade 1[d]

CRS = cytokine release syndrome; CT = computed tomography; ICU = intensive care unit; **IL-6 = interleukin-6;** IV = intravenous; MRI = magnetic resonance imaging**; PK = pharmacokinetic(s)**.

[a] Antifungal prophylaxis should be strongly considered in subjects receiving steroids for the treatment of CRS and/or neurotoxicity.

[b] For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

[c] Diagnostic lumbar puncture for grade 3-4 neurotoxicity; consider for grade 2.

[d] Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.

[e] 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 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), 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 160. Siltuximab may not be repeated in an individual subject that develops anaphylaxis to siltuximab, or gastrointestinal perforation after siltuximab.

[f] A subgroup analysis for subjects treated with siltuximab will be evaluated, including CRS outcomes, safety, and PK data.

12.15 Appendix 15. Approximate Blood Volume Collection



12.16 Appendix 16. Modified Toxicity Probability Interval Design (mTPI-2)

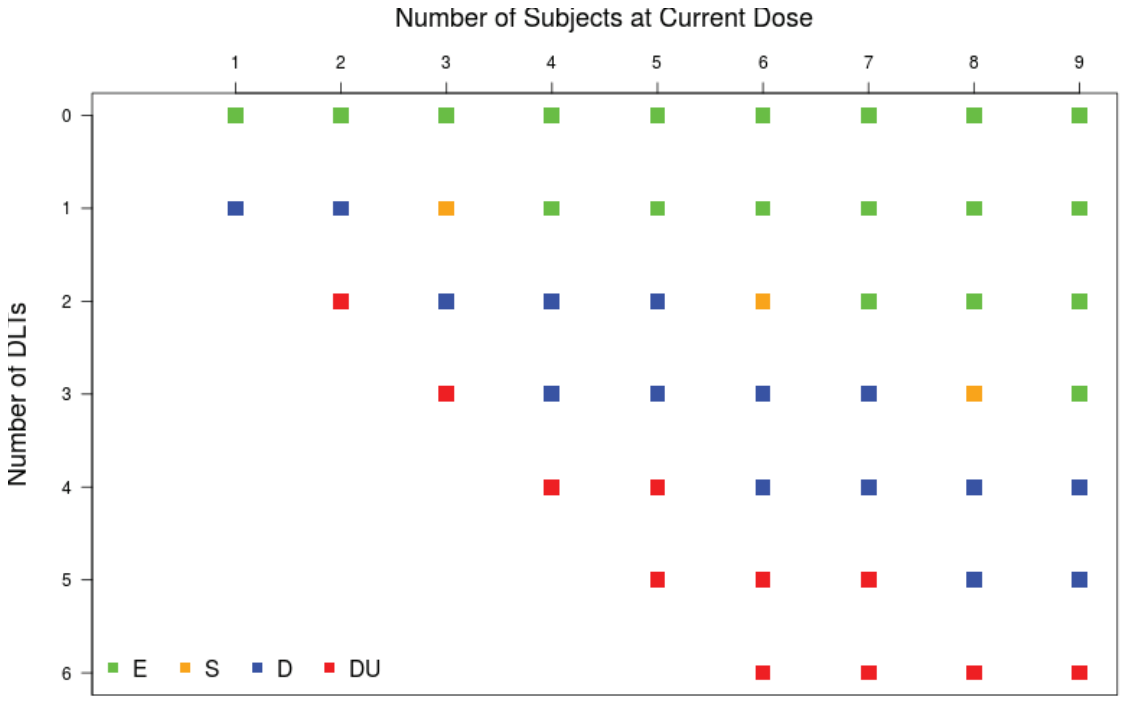
For Part 2 (AMG 160 Combination with pembrolizumab), trial monitoring rules are based on a modified toxicity probability interval design (mTPI-2). Prespecified monitoring rules are based on an extension of mTPI up-and-down design, mTPI-2, to determine the MTD with target DLT rate of 35% (Table 12-13). The mTPI-2 models the probability of toxicity for each dose level using a Bayesian model where each dose level has the same prior on the probability of toxicity, a Beta (1,1). The safety will be assessed based on mTPI-2 Dose Decision Outcomes with a [redacted]% Target DLT Rate. When subjects are treated at the current dose level, the posterior probability of toxicity is updated using the observed data from this level. Dose level decisions are made based on this posterior probability of toxicity, using 3 toxicity probability intervals (TPI).

[redacted]

For the current dose level and after adjusting for the width of the under-dosing TPI, if the DLT rate is most likely in the under-dosing TPI then the recommendation is to dose escalate. If the DLT rate is most likely in the target TPI then the recommendation is to stay at the current level. If the DLT rate is most likely in the over-dosing TPI then the recommendation is to de-escalate. If DLTs are observed, the maximum tolerated dose (MTD) is the dose level with a DLT toxicity rate closest to [redacted]%.

All subjects who are enrolled and receive at least 1 dose of AMG 160 in combination with pembrolizumab will be included in the analysis, unless otherwise specified. A formal interim analysis of available safety and efficacy data will occur when all remaining dose-escalation subjects have had the opportunity to complete 28 days on study. This interim analysis will estimate the MTD1 and MTD2 associated with the AMG 160 first step and target doses, support the determination of the RP2D, and support the evaluation of benefit/risk profile of AMG 160 plus pembrolizumab.

Table 12-14. mTPI-2 Trial Monitoring Table



E: Escalate to the next higher dose; S: Stay at the same dose; D: De-escalate to the previous lower dose; DU: De-escalate to the previous lower dose and the current dose will never be used again in the trial

12.17 Appendix 17. COVID-19 Guidance

- Subjects who test positive for coronavirus disease 2019 (COVID-19) using a test consistent with the institutional standard of care or who are exhibiting symptoms consistent with COVID-19 should not be enrolled in the study until complete resolution of symptoms.
- If an enrolled subject is exhibiting symptoms consistent with COVID-19, contact the Amgen Medical Monitor within 1 business day to ensure appropriate documentation and management of study activities.
- If a subject is unable to travel to the site for protocol-specified study visits and procedures, he/she can remain in the trial, provided that safety monitoring can occur. Alternatives, such as telemedicine to conduct visits, should be considered.
- On-site monitoring visits may be replaced by remote monitoring visits during COVID-19. Additionally, remote source document verification may be utilized for critical data points.
- Additional COVID-19 guidance from Food and Drug Administration (FDA) and European Medicines Agency (EMA) should be followed in consultation with Amgen medical monitor.

Amendment 10

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 16 March 2022

Rationale:

[redacted]

- Remove references of participation by European sites in Part 6, Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort.

[redacted]

[redacted]

- Update adverse event and serious adverse event reporting and product complaint language throughout protocol to align with current Amgen protocol template.
- Make typographical, formatting, and editorial changes throughout the protocol.

Section: Global

Change:

Updated version date throughout the document from 26 August 2021 to **16 March 2022**.

Section: 1, Protocol Synopsis, Overall Design, Part 2: AMG 160 Combination with Pembrolizumab, first paragraph

Replace:

This combination dose exploration study will explore the safety, pharmacokinetics, and efficacy of AMG 160 in combination with the PD-1 inhibitor pembrolizumab in approximately 20 subjects with mCRPC (Figure 2-2).

With:

This combination dose exploration study will explore the safety, **PK**, and efficacy of AMG 160 in combination with the PD-1 inhibitor pembrolizumab in approximately **3**0 subjects with mCRPC (Figure 2-2).

Section: 1, Protocol Synopsis, Overall Design, Part 6: Cytochrome P450 (CYP) Cocktail Drug Interaction Cohort, last paragraph

Replace:

Part 6 will be conducted in US, Europe, and Singapore

With:

Part 6 will be conducted in **the** US and Singapore

Superseding Amendment 9

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number (AMG 160) 20180101

EudraCT Number: 2018-003301-26

NCT Number: NCT03792841

Amendment Date: 26 August 2021

Rationale:

This superseding protocol is being amended to:

- Clarify that disease progression assessment will be performed per PCWG3 guidelines alone instead of RECIST v1.1 with PCWG3 modifications.
- Clarify disease response endpoints.



- Rename the terminology “theoretical risk” to “potential safety concern” with no change to other classifications (identified risks and potential risks).



- Make editorial, abbreviation, formatting, and grammatical changes.

Amendment 9

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

2018-003301-26

Amendment Date: 18 June 2021

Rationale:

The rationale for this protocol amendment is to include the following updates:

- Two-step dosing has been removed throughout the protocol as this dosing strategy will no longer be pursued. Extended intravenous (eIV) dosing will be utilized in all parts of the study.



[redacted]

- In Part 2 (AMG 160 + Pembrolizumab), language was updated to indicate that an additional 10 subjects may be enrolled once the combination recommended phase 2 dose (RP2D) is established.
- Several new assessments have been added to the Schedule of Activities:

[redacted]

- Schedule of Activities (Tables 2-1 and 2-2) have been updated to only include Parts 1, 2, and 3 of the study. Parts [redacted] and Part 6 have independent Schedule of Activities tables.

[redacted]

- Section 3.2.2.1.4 (Clinical Experience) has been updated to reflect the most recently available data.

[redacted]

- Sections 3.3.3.2 and 3.3.3.3 have been updated to reflect recently identified risks for pembrolizumab and etanercept, respectively.
- For PSMA PET/CT scans, ^{18}F-DCFPyL has been added as an alternative to ^{68}Ga-PSMA-11 for sites in the United States.
- Delay of the next infusion in the re-start guidance of Table 7-9 has been clarified and updated from 72 hours to 7 days based on current safety profile.

[redacted]

[redacted]

- Removed the word “maintenance” when referring to the “target dose” (based on BiTE® platform program-wide terminology change)
- Removed the phrase “run-in” or "priming" when referring to the 3-day eIV infusion (based on BiTE® platform program-wide terminology change)
- Updated to include guidance relating to coronavirus disease 2019 (COVID-19):
  - Eligibility criteria was updated to exclude subjects that have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
  - Guidance for COVID-19 vaccinations was added (Sections 7.8.2 and 7.8.2.6)
  - Table 7-9 was updated to include management for subjects with asympotomatic and symptomatic SARS-COV-2 infection and COVID-19 disease
- Several sections of the protocol have been updated to include required alignments with current Amgen protocol template (Sections 1.3, 7.1.6, 9.2.3.1.1.3, 9.2.3.1.1.4, 12.2, 12.3, and 12.4).
- Administrative and editorial changes (including grammatical, typographical, and formatting) have been made throughout the protocol.

Amendment 8

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 14 October 2020

Rationale:

Amendment 8 of the protocol was finalized on 14 October 2020 and was amended to include minor modifications to the Schedule of Activities that were erroneously omitted during finalization of Amendment 7, as well as a statement pertaining to collection of medical history. The bolding indicating new changes within the study protocol are inclusive of both Amendment 7 and Amendment 8.

Amendment 7 of the protocol was finalized on 30 September 2020 and was amended to:

[redacted]

- Add [redacted] and 6 to the study

[redacted]

[redacted]

- Schedule of Activities have been updated to reduce assessments wherever possible (reduced number of triplicate electrocardiograms, reduced blood sample collections for biomarkers and pharmacokinetics)
- Updated AMG 160 clinical summary with most recent data
- Several clarifications have been made throughout the protocol:

  [redacted]

  – planned doses for dose exploration has been expanded upon based on current plans

  – timing of vital sign assessments for different dosing schedules and parts of study

  [redacted]

  – study schemas, subject numbers, statistical considerations, and eligibility criteria have been updated to reflect new parts of study
- Additionally, administrative and editorial (typographical, grammatical, formatting) changes have been made throughout protocol.

Amendment 7

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 30 September 2020

Rationale:

This protocol is being amended to:

[redacted]

- Add [redacted] and 6 to the study

[redacted]

[redacted]

  - prophylactic intravenous (IV) hydration (per investigator discretion) to mitigate hypotension for the first dose of AMG 160

- Schedule of Activities have been updated to reduce assessments wherever possible (reduced number of triplicate electrocardiograms, reduced blood sample collections for biomarkers and pharmacokinetics)
- Updated AMG 160 clinical summary with most recent data
- Several clarifications have been made throughout the protocol:
  - [redacted]
  - planned doses for dose exploration has been expanded upon based on current plans
  - timing of vital sign assessments for different dosing schedules and parts of study
  - [redacted]
  - study schemas, subject numbers, statistical considerations, and eligibility criteria have been updated to reflect new parts of study
- Additionally, administrative and editorial (typographical, grammatical, formatting) changes have been made throughout protocol.

Amendment 6

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 05 May 2020

Rationale:

This protocol is being amended to:

- Add Parts 3 and [redacted] to the study.
  - Part 3 (etanercept prophylaxis for AMG 160-related cytokine release syndrome [CRS]): Part 3 will determine whether prophylaxis with the tumor necrosis factor alpha (TNF-α) inhibitor etanercept might decrease the frequency and severity of CRS without compromising the efficacy of AMG 160.

[redacted]

- Remove “medications known to cause QTc prolongation” as an excluded treatment during the study period. Based on safety data collected to date, the use of QTc prolongation medications are not expected to worsen AMG 160-related safety events.

[redacted]

- Add guidance for immune-effector cell-associated neurologic syndrome (ICANS) similar to that provided for CRS and tumor lysis syndrome (TLS). While the grading system has been developed in large part from chimeric antigen receptor T cells (CAR-T) therapies, symptoms of ICANS may be shared among immune effector-cell associated therapies such as bispecific T-cell engager (BiTE) molecules.
- Additionally, administrative and editorial (typographical, grammatical, formatting) changes have been made throughout protocol.

Amendment 5

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 05 December 2019

Rationale:

Protocol Amendment 5 provides additional mitigations for the management and mitigation of cytokine release syndrome, including implementation of 3 step dosing as well as continuous IV infusion of AMG 160 on C1D1. The following updates were made to the protocol dated 04 September 2019 :

- To mitigate cytokine release syndrome (CRS) and accelerate ramp up to efficacious doses in cycle 1, additional options for DLRT recommendations were introduced based on safety data from previously completed cohorts including:
  - Introduce 3-step dose schedule of assessments
  - Cycle 1 dosing schedule may be adapted to enable 3 day continuous IV infusion for C1D1
  - Mandate prophylaxis with tocilizumab (4-8 mg/kg single dose), IV hydration (1L normal saline), acetaminophen (975 mg single dose)
- Reduce schedule of assessments based on observed safety data (ie, reduce required blood collections for patients and ECG monitoring)

[redacted]

- Allow opening 2 or more cohorts at a given dose level (eg. involving different dose steps) simultaneously

[redacted]

- Incorporate changes to protocol amendment #4 required by VHP related to pembrolizumab combination study
- In addition, clarifications and corrections, inconsistencies, administrative and typographical changes were made throughout the protocol.

Amendment 4

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 04 September 2019

Rationale: The following updates were made to the protocol, dated 19 July 2019:

- Revised language to describe AMG 160 monotherapy as Part 1 of the study
- Added Part 2 to evaluate the safety and tolerability of AMG 160 in combination with pembrolizumab in adult subjects

[redacted]

- Added language to allow for backfill enrollment during Part 1 to better estimate the RP2D and better characterize the safety, efficacy, PK, and pharmacodynamics of AMG 160 monotherapy
- Added relevant information regarding pembrolizumab throughout various sections of the protocol (eg, risks, description and dosing regimen)
- Added Section 7.1.1.2 to state that ^{68}Ga-PSMA-11 and ^{18}F-FDG are non-Amgen investigational products to accommodate applicable local safety reporting requirements
- Added additional assessments for when intra-subject dose escalation is implemented
- Ensured consistency in terminology used to describe BiTE molecules
- In addition, clarifications and corrections, inconsistencies, administrative and typographical changes were made throughout the protocol.

Amendment 3

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 19 July 2019

Rationale: The following updates were made to the protocol, dated 15 February 2019:

- Updated protocol per recommendations by the Dose Level Review Team (DLRT) below:
  - Modified premedication regimen by implementing oral dexamethasone (or equivalent) 6-16 hours in addition to dexamethasone IV (or equivalent) within 1 hour prior to AMG 160 in cycle 1
  - Added language that DLRT may modify premedication dosing regimen based on emerging safety data
  - Clarified that a dose level review meeting (DLRM) may be triggered when at least 3 subjects in the cohort have received the full planned dose for the first cycle and have been followed for safety events for a minimum of 28 days from the first dose of AMG 160
  - Clarified that subjects on prior ^{177}Lu-PSMA-617 therapy may be eligible if discussed with Amgen medical monitor prior to enrollment
  - Clarified language regarding re-start guidance and permanent discontinuation due to adverse events in Table 7-5
- Clarified language describing single-step-dosing that the DLRT will recommend the initial run-in dose (MTD1), which will not be greater than the dose where a CRS of grade 2 or higher is observed
- Added language that describes the process and changes in schedule of activities for two-step-dosing if recommended by the DLRT
- Updated adverse event reporting language to reflect that only serious disease-related adverse events will be reported as per Amgen's standard processes.
- Clarified that ^{68}Ga PSMA PET/CT and ^{18}F-FDG PET/CT, if considered as investigational agent, are not excluded while participating in this study
- Added language that a safety follow-up visit will be performed approximately 30 (+3) days after the end of the last dose of investigational product or prior to initiation of other therapy, whichever occurs first
- Refined statistical language regarding sample size determination

- Added window for PK collection times
- Added approximate blood volume collection table per study period
- Increased number of sites and included Asia to the geographic regions for the study
- In addition, clarifications and corrections, inconsistencies, administrative and typographical changes were made throughout the protocol.

Amendment 2

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

Amgen Protocol Number AMG 160 20180101

Amendment Date: 15 February 2019

Rationale:

The following updates were made to the protocol, dated 20 November 2018:

- Updated per comments on the response to the VHP application for the study including but not limited to:
  - Clarified hypothesis
  - Clarified the Study Schema figure to incorporate when dose decisions will be made
  - Added safety stopping rules
  - Restricted to ECOG 0-1 (previously 0-2)
  - Excluded venous thrombosis (in addition to arterial thrombosis)
  - Clarified DLT definition with regards to fever
  - Clarified CRS definition
- Implemented dexamethasone premedication prior to all AMG 160 doses in cycle 1
- Clarified safety reporting language for study-mandated procedures including ^{68}Ga-PSMA-11 imaging
- Clarified windows for collection time prior to dosing for PK (up to 30 min) and safety labs (up to 24 hours)
- Clarified that bone scans must be ^{99m}technetium methylene diphosphonate or ^{99m}technetium hydroxydiphosphonate single-photon emission computed tomography (^{99m}Tc-MDP SPECT or ^{99m}Tc-HDP SPECT).
- Added that during dose expansion, samples found to be positive for binding antibodies will be assessed for clinical impact to drug exposure and subject safety.
- In addition, clarifications and corrections of inconsistencies, and administrative and typographical changes were made throughout the protocol.

Amendment 1

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Prostate Specific Membrane Antigen Half-life Extended Bispecific T-cell Engager AMG 160 in Subjects With Metastatic Castration-resistant Prostate Cancer

AMG 160

Amgen Protocol Number AMG 160 20180101

Amendment Date: 20 November 2018

Rationale:

The following updates were made to the protocol, dated 20 November 2018:

[redacted]

- Clarified Table 2-1 Schedule of Activities that end of infusion (EOI) assessments or procedures are to be completed after the AMG 160 post-infusion flush as defined by the IPIM
- For Table 12-1 changed:
  - PT to APTT
  - PTT/INR to PT/INR
- Typographical errors and inconsistencies between sections and throughout the protocol were corrected

Approved