Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 211 Administered as Continuous Intravenous Infusion in Subjects With Relapsed/Refractory Gastrointestinal Adenocarcinoma

AMG 211

Amgen Protocol Number (AMG 211) 20130354

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Investigator's Agreement

I have read the attached protocol entitled "A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 211 Administered as Continuous Intravenous Infusion in Subjects with Relapsed/Refractory Gastrointestinal Adenocarcinoma", dated 10 May 2016 and agree to abide by all provisions set forth therein.

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

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Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 211 Administered as Continuous Intravenous Infusion in Subjects with Relapsed/Refractory Gastrointestinal Adenocarcinoma

Study Phase: 1

Indication: Relapsed/refractory gastrointestinal (GI) adenocarcinomas known to express carcinoembryonic antigen (CEA)

Primary Objectives:

- Evaluate the safety and tolerability of AMG 211 in adult subjects with relapsed/refractory GI adenocarcinomas
- Determine the maximum tolerated dose (MTD) and/or biologically active dose (eg, recommended phase 2 dose)

Secondary Objectives:

- Describe the pharmacokinetics (PK) of AMG 211
- Determine the formation of anti-AMG 211 antibodies
- Evaluate time to progression and to evaluate the proportion of subjects progression-free at 6 months
- Evaluate the anti-tumor activity of AMG 211 by evaluating
  - The number and proportion of subjects with objective response according to the modified Immune-related Response Criteria (irRC)
  - The duration of response and time to response

Exploratory Objectives:

- Evaluate the protein, nucleic acid, and cellular biomarkers in blood (eg, cytokines, lymphocyte subsets) before and following treatment with AMG 211
- Evaluate the effects of genetic variations in cancer genes
- Evaluate multiple other aspects of the tumor and tumor microenvironment before and following treatment with AMG 211, which may include CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes

Hypotheses: Objective responses according to modified irRC will be observed at dose levels that achieve acceptable safety and tolerability.

Primary Endpoint:

- Safety: subject incidence of treatment emergent adverse events (TEAEs), dose-limiting toxicities (DLTs), and clinically significant changes in vital signs, electrocardiograms, physical examination findings, and clinical laboratory tests

Secondary Endpoints:

- PK of AMG 211 after continuous intravenous (cIV) infusion across 2 cycles
- Incidence of anti-AMG 211 antibody formation
- Time to progression (TTP)
- 6-month progression-free rate
- Efficacy parameters: overall response rate (ORR; per modified irRC), duration of response, time to response

Exploratory Endpoints:

- Changes in methylation and mutations in circulating free DNA present in plasma
- Lymphocyte counts, T-cell activation, and immune checkpoint regulator status

- Changes in serum cytokine levels
- Biomarkers and mutations in tumor cells
- Changes in circulating tumor cells (CTCs)
- Soluble CEA serum levels

Study Design: This is a multi-center, open-label, sequential dose-escalation study evaluating AMG 211 as cIV infusion in adult subjects who have relapsed/refractory GI adenocarcinoma. This study will be conducted in two parts:

- Dose-escalation:

  The dose-escalation will define the MTD, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 211.
- Dose-expansion:

  The dose-expansion will enroll additional subjects to gain further clinical experience with AMG 211.

Dose-escalation:

In dose-escalation cohorts, the planned dose levels are as follows: 200, 400, 800, 1600, 3200, and 6400 µg/day. Alternative dose levels up to 12800 µg/d will be explored in either the 14-day or 28-day schedule based on emerging data. See Section 6.2.1 for complete information.

Dose escalation decisions will consider the incidence of DLTs among DLT-evaluable subjects.

The DLRT may consider the modeling of the dose escalation complete if 1 of the following rules is met:

- The highest planned dose level is evaluated and no DLTs occur at any dose level. In this case the maximum administrated dose will be used in a dose-expansion cohort
- The toxicity probability interval (TPI) Bayesian model recommends the same dose 3 times (not necessarily sequentially)
- A total of approximately 39 DLT-evaluable subjects have been enrolled

Dose-Expansion:

Approximately 39 subjects will be enrolled in the dose-expansion cohort to gain further clinical experience with AMG 211. Of those, approximately 29 subjects will participate in a parallel imaging study sponsored by the University Medical Center Groningen and conducted in the Netherlands, hereafter referred to as the Imaging Study. Multiple dose levels will be evaluated in the dose-expansion cohort. Subjects not participating in the Imaging Study will start enrollment into the dose-expansion cohort upon completion of the dose-escalation cohorts and will be treated using the MTD or recommended phase 2 dose. Subjects concurrently participating in the Imaging Study may start enrollment into the dose-expansion cohort while dose-escalation cohorts are still open for enrollment. These subjects will be treated at the MTD or recommended phase 2 dose or at a lower dose.

A final estimate of the recommended phase 2 dose will be based on the TPI Bayesian model using all DLT-evaluable subjects of the dose-escalation and the dose-expansion cohort.

Sample Size: It is anticipated that approximately 78 subjects will be enrolled in this study. Approximately 39 subjects will be enrolled in the dose-escalation cohorts and approximately 39 additional subjects will be enrolled in the dose-expansion cohort. The sample size of the dose-escalation cohorts is determined empirically and is consistent with this type of study using a modified TPI Bayesian model design.

Summary of Subject Eligibility Criteria: Male or female subjects ≥ 18 years of age at the time of informed consent who have pathologically documented, GI adenocarcinoma (including but not limited to esophageal, gastric, small intestine, colorectal, or pancreatic cancers) that has failed standard treatments or for which standard curative or palliative measures do not exist or are no longer effective are eligible for this study. Subjects must have at least 1 measurable tumor lesion

per the modified irRC (Appendix D) and adequate hematological, renal, and liver function. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: AMG 211 will be presented as a sterile, single-use, lyophilized formulation for cIV infusion in a 3 mL glass vial containing 0.37 mg AMG 211. The intravenous (IV) bag protectant will be presented as a sterile liquid in a 20 mm glass vial (containing 10 mL of IV bag protectant) intended for pre-treatment of IV bags prior to dilution of AMG 211 drug product. AMG 211 infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines. The investigational product will be administered as a cIV infusion. Subjects will be hospitalized on day 1 cycle 1 for a minimum of 72 hours and at all subsequent cycles for a minimum of 48 hours. If required for logistical reasons (eg, long travel times), subjects may be hospitalized the day before dosing (day -1) of any cycle and at the end of infusion for cycle 1 for required PK samples. Subjects in the 7- and 14-day schedules will receive AMG 211 for 7 or 14 days followed by 21 days off or 14 days off, respectively (a 28-day cycle). Subjects on a 28-day schedule will receive AMG 211 for 28 days followed by 14 days off (a 42-day cycle).

Procedures: After providing informed consent, eligible subjects will undergo the following assessments during this study: clinical evaluation (physical examination, Karnofsky Performance Status, height, and weight), vital signs, pulse oximetry, laboratory assessments (chemistry, hematology including coagulation, urinalysis, hepatitis serology, human immunodeficiency virus (HIV), tumor markers, and anti-AMG 211 antibody), radiological assessments to evaluate disease and response, biomarker assessments, and PK assessments. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedules of Assessments (Table 6, Table 7, and Table 8).

Statistical Considerations: The following data analyses are planned: (1) dose decision analyses in the dose-escalation cohorts after every 3 DLT-evaluable subjects, (2) a safety review of dose escalation after all subjects in dose escalation have had the opportunity to complete 6 months of treatment, (3) the primary analysis after all dose-escalation and dose-expansion subjects have completed 6 months of treatment, and (4) the final analysis after all subjects have ended the study.

The DLRT is responsible for all dose level decisions during dose escalation. Dose decisions are planned after every 3 to 6 subjects are enrolled throughout the dose-escalation cohorts. The DLRT considers the recommendation for subsequent doses based on the following rules:

- Based on the modified TPI Bayesian model, the next dose is the one with the highest probability of the target TPI (0.20, 0.35), but with a less than 0.25 probability of an excessive or unacceptable TPI.
- If ≥ 1 subject has a DLT at a dose level, then the dose escalation cannot occur unless there are 6 or more DLT-evaluable subjects at that dose level. However, if a transient cytokine-release syndrome is reported as the DLT, but resolves within 48 hours and can be managed with prophylactic corticosteroids, the DLRT may decide to escalate the dose with the institution of prophylactic corticosteroid administration.
- The maximum allowed dose increase will be 1 dose level above the maximum of previous evaluated doses.
- Dose escalation can be achieved by evaluating a higher dose level with the same infusion duration (eg, 800 µg/day for 14 days to 1600 µg/day for 14 days), or by evaluating the same dose level with a prolonged infusion duration (eg, from 800 µg/day for 14 days to 800 µg/day for 28 days). The DLRT may also decide to explore in parallel both options mentioned above after the dose escalation decision is made, or to prioritize one schedule. In this case, 2 TPI models may be run in parallel to obtain dose recommendations for these 2 schedules separately.
- Intermediate dose levels not pre-specified may be considered based on the optimal dose recommended by the TPI model.

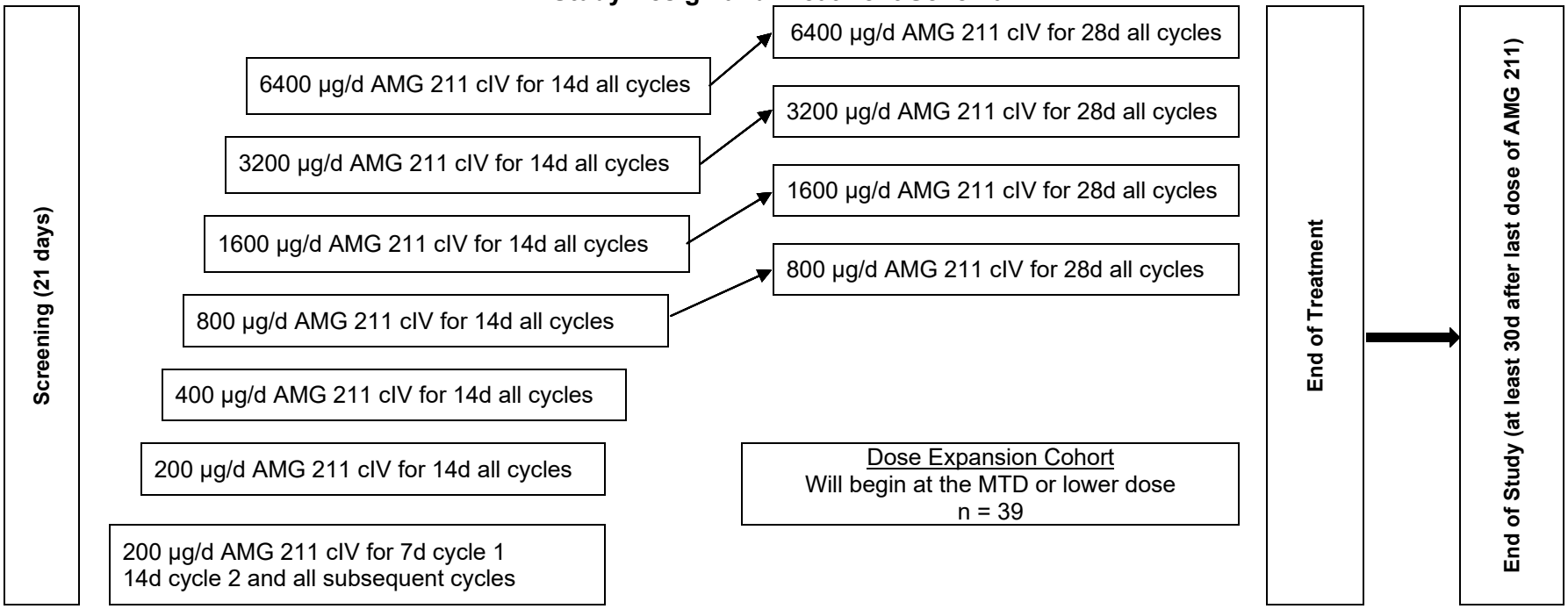
The Amgen Medical Monitor (or EDL) and Amgen Global Safety Officer can make dose decisions without convening the DLRT in the following limited circumstances:

- If a cohort has at least 3 DLT-evaluable subjects and 1 subject experiences a DLT, then the Amgen Medical Monitor and Amgen Global Safety Officer may decide to expand the number of subjects treated in this cohort.
- The Amgen Medical Monitor (or EDL) and Amgen Global Safety Officer may decide to open the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated by the DLRT.

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

Sponsor: Amgen, Inc.

Study Design and Treatment Schema*



AMG 211 7-day & 14-day Schedule
- 7 days cIV dosing followed by 21 days off treatment (28-day cycle) cohort 1/cycle 1 only
- 14 days of cIV dosing followed by 14 days off treatment (28-day cycle)
- DLT window is 28 days in all cohorts
- 7 nominal dose levels with potential alternative doses
- The TPI Model may propose a new dose after occurrence of the first DLT; decision by DLRT
- n = 3 to 6

AMG 211 28-day Schedule
- 28 days cIV dosing followed by 14 days off treatment (42-day cycle) for cycle 1
- DLT window is 28 days in all cohorts
- Expansion to the 28-day schedule will be determined by DLRT
- The TPI Model may propose a new dose with a 14-day infusion and/or a new dose for a 28-day infusion; decision by DLRT
- Cohorts with 28-day and 14-day schedule can run in parallel or one schedule can be prioritized
- n = 3 to 6

* Depending on the safety data from the 6400 µg/day cohorts, a level of 12800 µg/day can be added, if agreed by the DLRT. The longest schedule allowing highest dose intensity (14-day or 28-day infusion) found to be tolerated will be selected for the additional cohort.
cIV = continuous intravenous; d = day; DLRT = dose level review team; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; TPI = toxicity probability interval

Study Glossary

Abbreviation or Term	Definition/Explanation
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from time zero to infinity
BiTE®	Bispecific T-cell engager
BLQ	Below limit of quantification
$C_{24\ hr}$	Plasma concentration observed after 24 hours
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CEACAM	CEA-related cell adhesion molecule
CI	Confidence interval
cIV	Continuous intravenous
CL	Systemic clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRC	Colorectal cancer
CRS	Cytokine Release Syndrome
C_{ss}	Steady-state drug concentration in plasma during constant-rate infusion
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCs	Circulating tumor cells
Dex	Dexamethasone
DILI	Drug-induced liver injury
DLRM	Dose Level Review Meeting
DLRT	Dose Level Review Team
DLT	Dose-limiting toxicity (for definition refer to Section 6.2.1.3)
DNA	Deoxyribonucleic acid
EC_{50}	50% of the maximal effective concentration level
EC_{90}	90% of the maximal effective concentration level
EDC	Electronic data capture
EDL	Early Development Lead
ECG	Electrocardiogram
eCRF	Electronic case report form

Abbreviation or Term	Definition/Explanation
End of Study (primary completion)	Defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint(s).
End of Study for Individual Subject	Defined as the last day that protocol-specified procedures are conducted for an individual subject
EOI	End of infusion
EOS	End of Study - Defined as when the last subject is assessed or receives an intervention for evaluation in the study; if the study includes multiple parts (eg, safety follow-up or survival assessment), the end of study would include these additional parts
EOIP	End of Investigational Product. Defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
EpCAM	Epithelial cell adhesion molecule
eSAE	Electronic serious adverse event (form)
FIH	First in human
GCP	Good Clinical Practice
GI	Gastrointestinal
Heart rate	Number of cardiac cycles per unit of time
HepBsAg	Hepatitis B surface antigen
HepCAb	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IPIM	Investigational Product Instruction Manual
IQR	Interquartile range
IRB	Institutional Review Board
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irRC	Immune-related Response Criteria
irSD	Immune-related Stable Disease
IV	Intravenous
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Not available
ND	Not done
NHL	Non-Hodgkin’s lymphoma

Abbreviation or Term	Definition/Explanation
ORR	Overall response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
Q2C	Every 2 cycles
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
RNA	Ribonucleic acid
RR interval	The time elapsed between 2 consecutive R waves as measured by ECG
sCEA	Soluble carcinoembryonic antigen
SCR	Screening
SD	Standard deviation
Source Data	Information from an original record or certified copy of the original record containing 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.
SPD	Sum of the products of the 2 longest perpendicular diameters
Study day 1	Defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2}$	Terminal-phase elimination half-life
TBL	Total bilirubin
TEAEs	Treatment Emergent Adverse Events
Th17	T-helper 17
TPI	Toxicity probability interval
Treg	Regulatory T-cells
TTP	Time to progression
UE	Unable to evaluate
ULN	Upper limit of normal
V_{ss}	Apparent volume of distribution at steady state

Abbreviation or Term	Definition/Explanation
WBC	White blood cell
WHO	World Health Organization

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

1. OBJECTIVES

1.1 Primary

The primary objectives of this study are to:

- Evaluate the safety and tolerability of AMG 211 in adult subjects with relapsed/refractory gastrointestinal (GI) adenocarcinomas
- Determine the maximum tolerated dose (MTD) and/or biologically active dose (eg, recommended phase 2 dose)

1.2 Secondary

The secondary objectives of this study are to:

- Describe the pharmacokinetics (PK) of AMG 211
- Determine the formation of anti-AMG 211 antibodies
- Evaluate time to progression (TTP) and evaluate the proportion of subjects progression-free at 6 months Evaluate the anti-tumor activity of AMG 211 by evaluating
  - The number and proportion of subjects with objective response according to the modified Immune-related Response Criteria (irRC)
  - The duration of response and time to response

1.3 Exploratory

The exploratory objectives of this study are to:

- Evaluate the protein, nucleic acid, and cellular biomarkers in blood (eg, cytokines, lymphocyte subsets) before and following treatment with AMG 211
- Evaluate the effects of genetic variations in cancer genes
- Evaluate multiple other aspects of the tumor and tumor microenvironment before and following treatment with AMG 211, which may include carcinoembryonic antigen (CEA) expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes

2. BACKGROUND AND RATIONALE

2.1 Disease

CEA is a glycosylated human oncofetal antigen that belongs to the CEA-related cell adhesion molecule (CEACAM) family of the immunoglobulin gene superfamily. Within this superfamily, CEA is defined as CEACAM5, but CEA is the more commonly used abbreviation. This gene is also designated in cluster of differentiation (CD) nomenclature as CD66e. CEACAM5 is closely related to CEACAM1, CEACAM3, CEACAM4, CEACAM6, CEACAM7, and CEACAM8. CEA has been suggested to mediate homophilic and heterophilic cell to cell adhesion, facilitate bacterial colonization of the intestine, and protect the colon from microbial infection by binding and trapping

infectious microorganisms. Moreover, CEA attributes to signal transduction and interaction with proto-oncogenes in regulation of proliferation and cellular transformation (Hammarström, 1999).

In normal adult tissue, CEA expression can mainly be found on the apical border of columnar/epithelial cells of the colon, small intestine, stomach, pancreatic ducts, secretory cells of sweat glands, as well as the squamous epithelial cells of the uterine cervix, esophagus, and tongue and in the uroepithelium. CEA is a membrane component of adenocarcinoma of the GI tract and was one of the first identified tumor associated antigens (Gold and Goldenberg, 1997). Its expression is up regulated in many types of carcinoma. CEA is expressed in epithelial cell membranes and to smaller amounts in the cytoplasm of the cells in almost all cases of colorectal adenocarcinoma, and in a high proportion of adenocarcinomas of the salivary glands, esophagus, stomach, biliary tract, pancreas, and small intestine (Zheng et al, 2011; Vrabie et al, 2008; Sanders et al, 1994).

Current treatment for patients with advanced adenocarcinomas of the GI tract is rarely curative after the disease has advanced and metastasized, and survival is usually limited to a few months or years (Wu and Sung, 2013). These patients have a major unmet medical need, and urgently require new treatment options. Pancreatic cancer, colorectal cancer (CRC), gastric, and gastroesophageal cancer comprise a high prevalence of CEA expression of > 90% described in respective tumor samples (Peng et al, 2012) accounting for the population of this study. Interestingly, differences in T-cell infiltration have been reported in these tumor types. Patients with CRC have relatively high levels of infiltration with a favorable prognosis associated with this feature independent of tumor stage (Galon et al, 2006); whereas patients with pancreatic cancer demonstrate reduced levels of circulating lymphocytes compared to healthy controls (Fogar et al, 2006) and lower levels of infiltration in a highly immunosuppressive environment (von Bernstorff et al, 2001). In gastric cancer, T-helper 17 (Th17) cells as well as regulatory T-cells (Treg) have been reported to accumulate in the tumor microenvironment in early stage disease. Th17 cell infiltration gradually decreased with disease progression, while Tregs increased (Maruyama et al, 2010). This may be important because T-cell infiltration may play a role in the activity of AMG 211 resulting in distinct anti-tumor activity depending on indication.

2.2 Amgen Investigational Product Background

AMG 211 is a novel, bispecific single-chain antibody of the bispecific T-cell engager (BiTE®) class that targets human CEA antigen (CD66e) on tumor cells and the CD3 epsilon (ε) subunit of the human T-cell receptor complex present on T-cells. AMG 211 is also referred to as MEDI-565 and MT111. The pharmacological action of BiTE® antibodies is based on their ability to mediate T-cell lysis of target-expressing cells.

The binding of AMG 211 to CEA and CD3 results in specific and selective T-cell-mediated killing of cancerous cells expressing CEA. However, AMG 211 effectively mediates the killing of cancer cells only if it binds concurrently to CEA on a tumor cell and to CD3 on a T-cell.

2.2.1 Nonclinical Pharmacology

AMG 211 specifically and selectively binds human CEA and cross-reacts with chimpanzee and cynomolgus monkey CEA. The BiTE® antibody binds with lower affinity to human CD3 than to human CEA, and cross-reacts with chimpanzee CD3, but not with cynomolgus monkey and mouse CD3.

The therapeutic action of the anti-CEA BiTE® antibody is mediated by the specific redirection of cytotoxic T lymphocytes to kill CEA-positive tumor cell. Concomitant binding of AMG 211 to CEA and CD3 over a wide range of effector-to-target cell ratios led to the activation of primarily $CD8^+$ T-cells and the subsequent redirected lysis of CEA expressing cells. In vitro cytotoxicity assays revealed that activation of T-cells by AMG 211 was specific and selective and resulted in a T-cell proliferation, increased cell surface expression of activation markers, and release of pro-inflammatory cytokines, perforin, and granzyme B. Importantly, AMG 211 did not induce the activation, proliferation, and cytokine release of T-cells in the presence of cells lacking expression of CEA.

AMG 211 monotherapy significantly inhibited tumor growth in a variety of in vivo xenograft models. The anti-tumor effect of AMG 211 requires the addition of human T-cells to immunocompromised mice used in the in vivo efficacy studies. For the tumor formation models, human effector and tumor cells were mixed prior to subcutaneous injection. AMG 211 treatment inhibited the tumor formation of cell lines established from colonic, pancreatic, lung, and stomach tumors.

AMG 211 treatment started immediately and 4 or 8 days after cancer cell injection followed by 4 additional consecutive daily doses. Tumor growth inhibition was

dependent on the presence of T-cells, required the expression of CEA on cancer cells, and was dependent on the daily recapitulation of treatment as well as on its duration.

Detailed information about the nonclinical pharmacology can be found in the current version of the MEDI-565/AMG 211 Investigator Brochure

2.2.2 Nonclinical Toxicology

AMG 211 is highly species specific, cross-reacting only with human and chimpanzee CD3. Cynomolgus monkey and mouse cross-reactive surrogate constructs were hampered by non-specific activity and different functional characteristics from AMG 211 rendering them non-informative for the performance of nonclinical toxicology studies.

Since no pharmacological relevant animal model exists for in vivo toxicity testing of AMG 211, the only relevant safety data are those obtained by MedImmune in the ongoing MI-CP216 (NCT012842331) first in human (FIH) study (Section 2.2.4).

Detailed information about the nonclinical toxicology and the safety strategy for AMG 211 can be found in the Investigator Brochure.

2.2.3 Clinical Pharmacokinetics

The PK of AMG 211 (MEDI-565) was evaluated in Study MI-CP216. AMG 211 was administered by intravenous (IV) infusion over 3 hours per day for 5 consecutive days (ie, days 1 through 5) every 28 days (defined as 1 cycle). PK data analyses were conducted for all cohorts. PK for cohorts at the 1.5 mg and 3.0 mg doses were analyzed with and without dexamethasone. Serum AMG 211 concentrations versus time profiles are shown in Figure 1. Pharmacokinetic parameters estimated by non-compartmental methods are shown in Table 1. Following IV infusion, the peak serum concentrations of AMG 211 increased approximately dose-proportionally from 0.5 µg/mL at the 0.75 µg dose level to 652.7 ng/mL at the 7.5 mg dose level. AMG 211 concentrations decreased rapidly after the end of infusion (EOI) with a short terminal elimination phase half-life of 2.2 to 6.5 hours. Clearance after the first dose ranged from 35 to 77 L/day, volume of distribution ranged from 5 to 12 L, and half-life ranged from 2 to 6.5 hours At the highest dose tested (7.5 mg), mean maximum plasma concentration (Cmax) at the EOI was 652.7 ng/mL, which decreased to 14.5 µg/mL within 24 hours. There was no notable accumulation between doses within a cycle and the PK was similar across cycles for a given dose. Trough concentrations at 24 hours post dose were below the limit of quantification (BLQ) in subjects receiving doses of 0.75, 2.25, 6.75, 20, and 60 µg (see Table 1). AMG 211 PK was comparable at 1.5 mg and 3 mg dose level with or

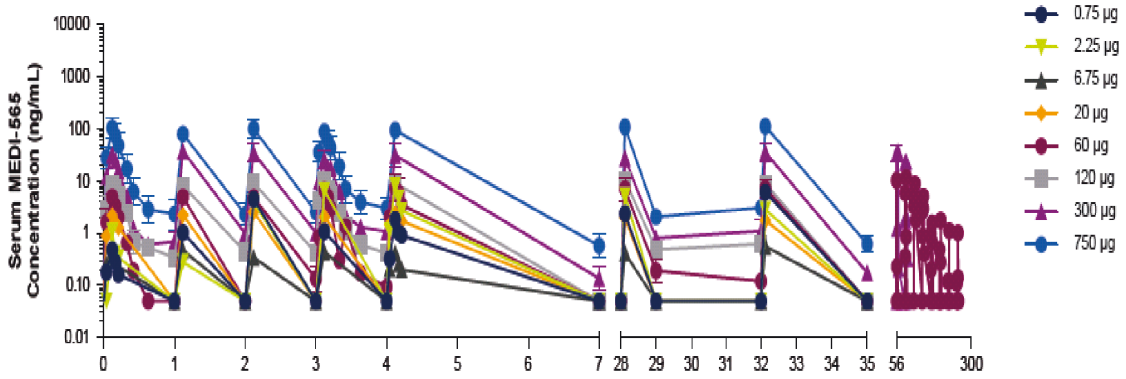
without dexamethasone co-administration, indicating dexamethasone had no effect on AMG 211 PK (see Table 1).

Figure 1. Mean MEDI-565/AMG 211 Serum Concentrations Following Repeated Intravenous Infusions in Patients With Gastrointestinal Adenocarcinomas

Pharmacokinetic profile of (A) low-dose cohorts (MEDI-565 0.75 µg–750 µg) and (B) high-dose cohorts (MEDI-565 1.5 mg–7.5 mg).

Abbreviation: DEX = dexamethasone.

A.



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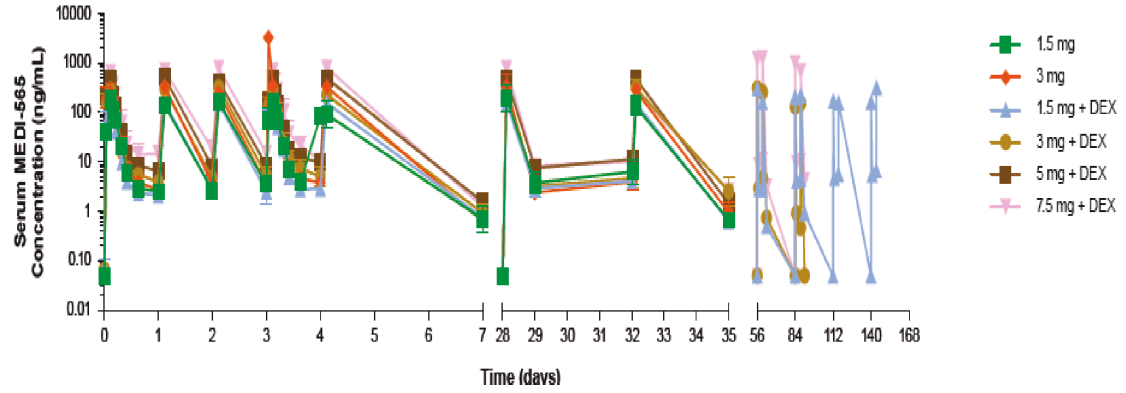

Table 1. Pharmacokinetic Parameters for MEDI-565/AMG 211 After First Dose

MEDI-565 Dose	n	Cmax (ng/mL) (SD)	C_{24h} (ng/mL) (SD)	AUC_{last} (ng•day/ mL) (SD)	AUC_{inf} (ng•day/ mL) (SD)	CL (L/day) (SD)	$t_{1/2}$ (hr) (SD)	V_{ss} (L) (SD)
0.75 µg	1	0.5 (NC)	NC	0.05 (NC)	NC	NC	NC	NC
2.25 µg	1	1.1 (NC)	NC	0.1 (NC)	NC	NC	NC	NC
6.75 µg	1	0.4 (NC)	NC	0.06 (NC)	NC	NC	NC	NC
20 µg	1	2.2 (NC)	NC	0.3 (NC)	NC	NC	NC	NC
60 µg	3	5.0 (0.9)	NC	0.7 (0.1)	0.8 (NC)	77.0 (NC)	2.2 (NC)	10.8 (NC)
120 µg	3	9.1 (2.6)	0.3 (0.1)	2.3 (0.3)	2.5 (0.02)	48.0 (0.4)	4.4 (1.2)	10.2 (3.5)
300 µg	3	31.8 (6.8)	0.7 (0.4)	9.0 (2.3)	9.1 (2.3)	34.5 (9.6)	3.5 (0.4)	5.2 (1.6)
750 µg	3	104.4 (58.4)	2.3 (2.3)	20.7 (11.9)	21.3 (12.4)	45.8 (28.9)	4.0 (0.6)	6.5 (2.3)
1.5 mg	3	180 (98.9)	2.6 (0.3)	30.1 (11.6)	30.6 (11.6)	53.9 (19.6)	3.5 (0.4)	8.6 (3.6)
3 mg	5	321.3 (102.0)	2.7 (0.1)	50.5 (9.3)	51.2 (9.3)	60.3 (11.8)	3.5 (1.5)	6.6 (2.0)
1.5 mg/ DEX	3	156.3 (11.8)	2.1 (0.6)	29.7 (9.7)	30.2 (9.8)	53.2 (16.7)	4.4 (1.2)	7.1 (2.6)
3 mg/ DEX	3	297.0 (68.8)	4.0 (1.1)	49.2 (6.1)	50.7 (7.0)	59.9 (7.7)	6.5 (2.5)	8.6 (0.3)
5 mg /DEX	6	506.2 (70.3)	6.4 (1.5)	80.3 (14.1)	82.1 (14.2)	62.3 (9.8)	5.0 (1.4)	8.9 (2.3)
7.5 mg/ DEX	3	652.7 (31.3)	14.5 (7.7)	108.3 (18.4)	111.2 (28.6)	69.8 (17.9)	5.3 (0.8)	12.0 (0.6)

Abbreviations: NC = not calculated
AUC_{inf} = area under the concentration-time curve from time zero to infinity; BLQ = below limit of quantification (< 0.1 ng/mL); $C_{24\ hr}$ = plasma concentration at 24 hours; C_{max} = maximum plasma concentration; Dex = dexamethasone; N = number of subjects; NA = not available; SD = standard deviation; V_{ss} = apparent volume of distribution at steady state

Based on linear PK, it is possible to predict exposure and PK profiles of the continuous intravenous (cIV) infusion dosing regimen. The average CL of 2.3 L/hr (ie, 55.2 L/day) and the average V_{ss} of 8.0 L observed in cohorts 1 to 11 from study MI-CP216 were used for simulation using a one-compartment PK model. The predicted AUC_{inf} and steady-state drug concentration in plasma during constant-rate infusion (C_{ss}) at any given cIV infusion dose of AMG 211 can be calculated using the following equations:

daily AUC_{inf} = daily dose/CL; $C_{ss} = R_o/CL$, where R_o is the dosing rate in µg/day. Predicted PK profiles and exposure after cIV dose rate of 200 to 12800 µg/day are shown below (Figure 2 and Table 2).

The starting dose of 200 µg/day in the cIV infusion study on AMG 211 would lead to an average total AUC_{inf} and C_{ss} per 14-day cycle of 1217 hr*ng/mL (ie, 51 day*ng/mL) and 3.6 ng/mL, respectively which is about 3-fold and 50-fold less than total AUC_{inf} (151 day*ng/mL) and C_{max} (180 ng/mL) observed per 5-day cycle at 1500 µg/day in study MI-CP216. In addition, the expected approximate cIV steady-state drug concentration for this starting dose (3.6 ng/mL) will be in the range of the highest drug concentration observed after 24 hours ($C_{24\ hr}$) with any 3-hour infusion (2.7 ng/mL) and will be in the range of the mean 50% of the maximal effective concentration level (EC_{50}) of the most sensitive GI cancer cell line (2 ng/mL).

The cIV infusion regimen would avoid fluctuation in exposure between C_{max} and the lowest concentration and would lead to stable C_{ss} which can provide adequate and sustained target coverage and may lead to less C_{max} driven toxicity.

Figure 2. Predicted Mean PK Profiles of AMG 211 After cIV Infusion Dosing of 200 to 6400 µg/day for 14 Days Using One-compartment Model With Average Clearance and Volume of Distribution of 2.3 L/hr and 8.0 L, Respectively

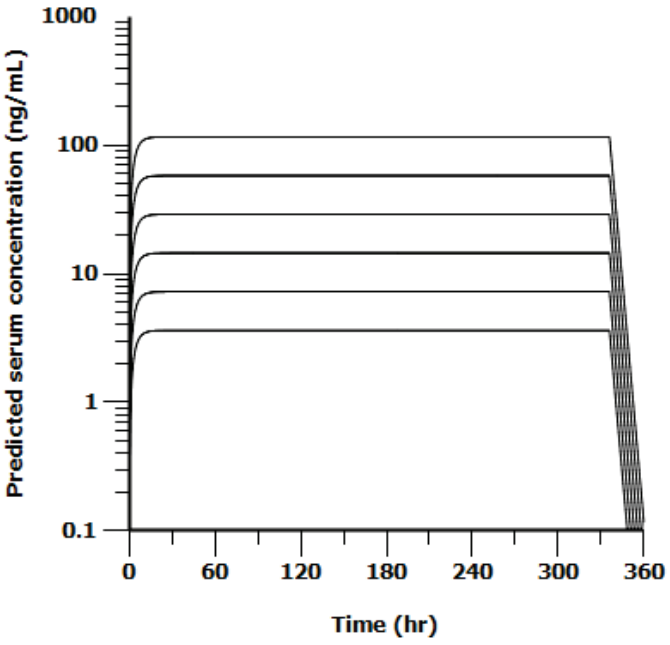

Table 2. Predicted Mean Exposure to AMG 211 After cIV Infusion Dosing of 200 to 12800 µg/day for 14 Days Using Average Clearance of 2.3 L/hr

Parameter	Dose (µg/day)						
	200	400	800	1600	3200	6400	12800
C_{ss} (ng/mL)	3,6	7,2	14,5	29	58	116	232
Total AUC per 14-day cycle (hr*ng/mL)[a]	1217	2435	4870	9739	19478	38957	77915
Daily AUC (hr*ng/mL)[b]	87	174	348	696	1391	2783	5565

AUC = area under the concentration-time curve; C_{ss} = steady-state drug concentration in plasma during constant-rate infusion
[a] Total AUC from zero to infinity over 14 days of dosing
[b] Calculated from total AUC divided by 14

2.2.4 Clinical Data From First-in-Human Study With MEDI-565/AMG 211

A phase 1 FIH study (MI-CP216) was conducted by MedImmune with MEDI-565/ AMG 211 in the United States. This was Phase 1, multicentre, open-label, single-arm dose-escalation and optional dose-expansion study to evaluate the safety, tolerability, PK, immunogenicity, and anti-tumor activity. In Study MI-CP216, AMG 211 was given by IV infusion over 3 hours per day for 5 consecutive days of a 28-day cycle (ie, short-term infusion) in adult subjects who had refractory gastrointestinal adenocarcinomas for which no standard or curative therapies are available. The study consisted of an initial dose-escalation phase to determine the maximum tolerated dose (MTD) or optimum biologic dose (OBD). The dose escalation phase was followed by an optional dose expansion phase at the MTD/OBD. However, in January 2015, the sponsor (MedImmune) made a decision not to start the dose-expansion phase of the study due to a lack of efficacy, as no objective response per the Response Evaluation Criteria in Solid tumors was observed. The decision to stop the study was not related to any safety issues.

Dose escalation proceeded from daily dose levels of 0.75 µg up to 3 mg/day. At the 3 mg/day dose level 2 dose-limiting toxicities (DLTs; grade 3 hypoxia within 12 hours of infusion start on day 1 in both subjects) were observed.

The study was amended to include administration of dexamethasone before MEDI-565/AMG 211 is administered (steroid prophylaxis) for presumed inflammatory/cytokine mediated toxicities. Dosing resumed in the amended study at

1.5 mg/day which was deemed tolerable. A cohort of 3 subjects has been exposed at 3 mg/day with steroid prophylaxis. These subjects all tolerated the infusion period without a DLT.

In total, four patients (2 at 3 mg and 2 at 7.5 mg + dexamethasone) experienced DLTs: hypoxia (n=2), diarrhea (n=1), and cytokine release syndrome (CRS; n=1). The MTD was determined to be MEDI-565 5 mg with dexamethasone premedication. The most common treatment-emergent adverse events were nausea, abdominal pain, vomiting, and fatigue. Grade 3 treatment-related adverse events were observed in 5 patients and included diarrhea, CRS, increased alanine aminotransferase, hypertension (all, n=1), and hypoxia (n=2). Six serious treatment-related adverse events were reported in 5 patients and included diarrhea, vomiting, pyrexia, CRS (all, 1 event), and hypoxia (2 events). Five patients were discontinued from treatment because of adverse events, including diarrhea, CRS, and central nervous system metastases (all, n=1), and hypoxia (n=2).

Nineteen patients (48.7%) had ADAs; 5 (12.8%) had high titers, 2 with decreased MEDI-565/AMG 211 concentrations. No objective responses occurred; 11 (28%) had stable disease as best response

Study 20130354 (phase 1) is the ongoing Phase 1 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of AMG 211 administered as continuous intravenous infusion (cIV) in subjects with relapsed/ refractory gastrointestinal adenocarcinoma. As of April 2016, approximately 32 subjects received AMG 211 for up to 6400 µg/cIV without any DLT.

2.2.5 Dosing Experience With Other BiTE® Antibodies

BiTE® antibodies exert a unique but also uniform mechanism of action independent from their respective target. Consequently, experiences with other BiTE® antibodies are regarded as being supportive for AMG 211 because of the limited nonclinical toxicity evaluation package for AMG 211.

CCI [redacted]

CCI [redacted]

A FIH study (MT110-101, EUDRACT 2007-004437-42, and NCT00635596) of solitomab has been conducted. An MTD has not yet been determined; however, DLTs have been observed in 9 subjects that include elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase, and bilirubin, as well as additional reports of abdominal pain, diarrhea, fever, and 1 report of supraventricular tachycardia. The safety profile of solitomab consists primarily of changes in laboratory values of liver function, peripheral edema, GI, and constitutional symptoms. Doses from 1 to 96 µg/day were administered to different cohorts. A typical cohort consisted of 1 to 2 cycles of treatment for 4 to 6 weeks each with a low starting dose run-in phase (3 µg/day in week 1, 12 µg/day in week 2 or 2 to 4) followed by a target dose on cycle 1 (weeks 3 to 6) or cycle 2. After IV infusion of solitomab, steady-state was reached quickly (within about 1 day), and C_{ss} values (mean ± standard deviation [SD]) were 3.27 ± 0.83, and 6.34 ± 0.41 ng/mL at the highest doses explored (48 and 96 µg/day). Respective C_{ss} values at a dose of 24 µg/day covered already the in vitro EC_{50} range (50 to 1000 pg/ml) and moreover, C_{ss} at a dose of 48 µg/day has reached the 90% of the maximal effective concentration level (EC_{90}) range of 1.4 to 3.8 ng/mL that was observed in CRC cell lines. Signs of antitumor activity have been described for some patients (eg, reduction in ascites, drop in circulating tumor cells [CTCs]) although, no objective response has been reported to date (Fiedler et al, 2012).

Clinical experience with a related BiTE® molecule called blinatumomab (AMG 103, MT103; specificity for CD3 and CD19) has shown that administration of BiTE® by cIV infusion can be performed with an acceptable safety profile and can lead to clinical responses in subjects with late-stage hematological malignancies (Nagorsen et al, 2012). In the adult relapsed/refractory non-Hodgkin's lymphoma (NHL) population, the most common clinical adverse events were flu-like symptoms such as fever, fatigue, weight changes, headaches, and chills. The most frequently reported adverse events of grade ≥ 3 were febrile neutropenia, neutropenia, leukopenia, anemia, thrombocytopenia, and pneumonia. Subjects receiving blinatumomab may experience a spectrum of neurologic and psychiatric events, such as seizure, encephalopathy, tremor, apraxia, speech disorders (aphasia, dysarthria), and disorientation. The incidence of

subjects experiencing neurologic and psychiatric events is greatest within the first few days of treatment with blinatumomab.

In preceding short-term infusion studies blinatumomab was tested at doses ranging from 0.75 to 13 µg/m², and was in all cases administered once, twice, or 3 times weekly as a 2- or 4-hour IV infusion. The most common adverse events were pyrexia, rigor, and fatigue. The most frequent laboratory abnormalities were mild-to-moderate changes in hematologic or coagulation parameters. All 3 short-term infusion studies were terminated early based on assessments of the overall benefit/risk profile. Neurologic adverse events, cytokine-release syndrome, and infections were observed in subjects in the absence of objective clinical responses or robust signs of biological activity such as a sustained reduction of peripheral $CD19^+$ B-cell (Nagorsen et al, 2012).

Consequently, in following studies in NHL subjects, blinatumomab was administered as a cIV infusion over a period of 4 or 8 weeks to guarantee a sustained presence of blinatumomab in serum at highly predictable drug levels over the entire infusion period, confirmed by PK analyses which also showed dose linearity. First complete responses to blinatumomab monotherapy, as assessed by Cheson criteria, were observed at a dose level of 15 µg/m² per day (Bargou et al, 2008). This dose level led to a sustained serum level of 0.6 to 1 ng/mL. Response rates of 83% (10/12 subjects) and 71% (5/7 subjects) were reported for follicular lymphoma and mantle cell lymphoma, respectively, although no objective responses have been seen in subjects treated below a dose of 15 µg/m² per day. The minimum required dose of 15 µg/m² per day exceeds approximately 10-fold the observed EC_{50} concentration of blinatumomab of 100 pg/ml (Dreier et al, 2002). In summary, the overall risk/benefit assessment comparing short term intermittent IV dosing of blinatumomab with cIV administration clearly favors the cIV administration because of proven and clinically relevant anti-tumor activity.

On the basis of the observations and experiences with solitomab and blinatumomab the rationale for dosing in this study was built.

2.3 Risk Assessment

At this time, there is limited clinical experience with AMG 211 in humans from one completed FIH study sponsored by MedImmune (study MI-CP216) and approximately 32 subjects enrolled in this ongoing study 20130354. Cytokine Release Syndrome (CRS) has been defined as an Important Identified Risks to date. Refer to the MEDI-565/AMG 211 Investigator's Brochure (Appendix A, Developmental Core Safety Information and to Section 5.4) for the list of the potential risks.

2.4 Rationale

Clinical experience with blinatumomab, a CD19-targeting BiTE®, indicated that sustained exposure through cIV infusion for a period of 14 to 56 days provided clinical efficacy and therapeutic benefit (Bargou et al, 2008) whereas short term intermittent IV dosing for 1 week failed to elicit either a pharmacodynamic (PD) response or clinical activity (Nagorsen et al, 2012). When the same doses as used in the intermittent short term infusion studies were administered by cIV infusion, target engagement was demonstrated and clinical activity was observed. This suggests that some toxicity may be attributable to C_{max}, but that a more constant, lower prolonged exposure may be needed for anti-tumor effects. The blinatumomab experience suggests that clinical activity is dependent on providing an adequate C_{ss} for a prolonged period of time to activate T-cell engagement directed against target cells and to maintain repeated cycles of target cell lysis.

Low concentrations of AMG 211 (0.1 to 1.0 ng/mL) were sufficient to mediate lysis of metastatic CRC cells from patients previously treated with chemotherapy by patient derived T-cells in ex vivo experiments. Moreover, the authors described a very slow onset of the killing, and the peak of tumor cell death was observed after 4 to 5 days that is untypical for a BiTE® mechanism of action (Osada et al, 2010).

The first phase 1 study of MEDI-565 /AMG 211 (MI-CP216 investigated a 3-hour infusion for 5 consecutive days of a 28-day cycle. While subjects were dosed at levels as high as 7.5 mg/day, no objective responses were observed.

The original assumption for this study was that trough levels exceeding the EC_{50} concentration of the most sensitive cancer cell line of 2 ng/mL were considered sufficient to sustain anti-tumor activity. No objective responses were observed although AMG 211 C_{max} serum levels of up to 652.7 ng/mL and trough levels of up to 14.5 ng/mL were achieved. In addition, approximately 80% of subjects (19/24 subjects) treated with up to a dose of 3 mg/day discontinued treatment after a maximum of 2 cycles because of disease progression.

Experience from the solitomab FIH study illustrated that in solid tumor indications, dose levels achieving exposure comparable to mean or median EC_{50} or even EC_{90} concentrations of relevant cancer cell lines might be needed to observe substantial anti-tumor activity translating into objective response. The same study provided evidence that target-related toxicity can already occur at lower doses or with shorter

drug exposure. Moreover, the short term infusion studies with blinatumomab reported a C_{max} dependent toxicity without objective responses (Nagorsen et al, 2012).

Consequently, it is expected that the cIV administration of AMG 211 will result in lower C_{max} concentrations than seen with the intermittent 5-day administration of a 3-hour infusion and provide a C_{ss} with potential effective exposure for a more prolonged duration. This route of administration is hypothesized to improve the efficacy of AMG 211 as continuous exposure beyond a threshold level required for anti-tumor activity and may result in higher clinical activity compared with intermittent exposure beyond the threshold. The therapeutic index may also be improved by the elimination of adverse events attributable to the higher C_{max} of the discontinuous administration but other adverse events due to the more prolonged exposure will need to be assessed.

2.5 Clinical Hypotheses

The hypothesis for this phase 1 study is that objective responses according to modified irRC will be observed at dose levels that achieve acceptable safety and tolerability.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a multi-center, open-label, sequential dose-escalation study evaluating AMG 211 as a cIV infusion in adult subjects who have relapsed/refractory GI adenocarcinoma. This study will be conducted in two parts:

- Dose-escalation:
  The dose-escalation will define the MTD, safety, tolerability, PK, and pharmacodynamics (PD) of AMG 211.
- Dose-expansion:
  The dose-expansion will enroll additional subjects to gain further clinical experience with AMG 211.

Dose-escalation:

In dose-escalation cohorts, the planned dose levels are as follows: 200, 400, 800, 1600, 3200, and 6400 µg/day. Alternative dose levels up to 12800 µg/day will be explored in either 14-day or 28 day schedule based on emerging data. See Section 6.2.1 for complete information.

Subjects in cohort 1 of the dose-escalation cohorts will receive AMG 211 for 7 days followed by 21 days off treatment (cycle 1). After completing cycle 1, if no DLTs are observed, all subjects in cohort 1 will be allowed to continue treatment with the same

dose of AMG 211, but the infusion duration will be 14 days followed by 14 days off treatment.

In the subsequent dose-escalation cohorts, AMG 211 will be administered at escalating doses in a 2 weeks on and 2 weeks off schedule. Based on the results, the Dose Level Review Team (DLRT) may choose to extend the infusion duration from 14 to 28 days (a 4 weeks on and 2 weeks off schedule) if the 14-day administration schedule has been well tolerated and the safety profile allows for a longer infusion duration, and no anti-tumor response has been observed in a 14-day administration schedule. Moreover, the DLRT may decide to enroll in parallel into a cohort with a 28-day treatment duration or to prioritize one infusion schedule.

Dose escalation decisions will consider the incidence of DLTs among DLT-evaluable subjects.

The DLRT may consider the dose escalation complete if 1 of the following rules is met:

- The highest planned dose level is evaluated and no DLTs occur at any dose level. In this case the maximum administrated dose will be used in a dose-expansion cohort
- The toxicity probability interval (TPI) Bayesian model recommends the same dose 3 times (not necessarily sequentially)
- A total of approximately 39 DLT-evaluable subjects have been enrolled

Dose-Expansion:

Approximately 39 subjects will be enrolled in the dose-expansion cohort to gain further clinical experience with AMG 211. Of those, approximately 29 subjects will concurrently participate in the Imaging Study. Multiple dose levels will be evaluated in the dose-expansion cohort. Subjects not participating in the Imaging Study will start enrollment into the dose-expansion cohort upon completion of the dose-escalation cohorts and will be treated using the MTD or recommended phase 2 dose. Subjects concurrently participating in the Imaging Study may start enrollment into the dose-expansion cohort while dose-escalation cohorts are still open for enrollment and will be treated at the MTD or recommended phase 2 dose or at a lower dose. Table 3 presents an overview of the study design.

Table 3. Study Design Overview

Part	Cohort	Dose Level	Number of Subjects
Dose Escalation [b]	1	200 µg/d for 7 days in cycle 1 200 µg/d for 14 days in cycle 2 and all subsequent cycles	3-6
	2	200 µg/d for 14 days in all cycles	3-6
	3	400 µg/d for 14 days in all cycles	3-6
	4	800 µg/d for 14 days in all cycles	3-6
	5	1600 µg/d for 14 days in all cycles	3-6
	6	3200 µg/d for 14 days in all cycles	3-6
	7	6400 µg/d for 14 days in all cycles	3-6
	8*	12800 µg/d for 14 or 28 days in all cycles	3-6
28-day Schedule	X-1[a]	Dose Level -1 of 14-day Schedule × 28 days	3-6
	X-2[a]	MTD × 28 days	3-6
Dose Expansion	A	MTD or lower dose or highest dose tested without reaching MTD	39

d = day; DLT = dose-limiting toxicity; DRLM = dose level review meeting; EC_{50} = 50% of the maximal effective concentration level; MTD = maximum tolerated dose; PD = pharmacodynamic; PK = pharmacokinetic

[a] Alternative dosing regimens (eg, 28-day infusions) may be explored after a DLRM decision based on 1) occurrence of DLT(s) or other emerging safety data; 2) PK/PD data demonstrating drug exposure that is in the range or above the mean EC_{50} concentration of 29 ng/mL; 3) absence of objective responses in the 14-day infusion schedule

[b] Approximately 6 subjects from the dose escalation cohorts will concurrently participate in the Imaging Study after completion of cycle 2 of cIV AMG 211 treatment.

* Alternative dose level up to 12800 µg/day will be explored in either 14-day or 28-day schedule based on emerging data.

Subjects will be treated with AMG 211 until confirmed disease progression per modified irRC (Appendix D), or intolerance of study treatment, or clinically significant deterioration of health status requiring discontinuation, whichever occurs first. Due to the mechanism of action of immune-enhancing therapies, subjects may experience an apparent enlargement of existing lesions or the appearance of new lesions prior to maximal clinical benefit of AMG 211.

A final estimate of the recommended phase 2 dose will be based on the toxicity probability interval (TPI) Bayesian model using all DLT-evaluable subjects of the dose-escalation and the dose-expansion. Refer to section 10.4.2 for details of the TPI Bayesian model.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

This study will be conducted at approximately 5 sites in Germany and the Netherlands. Additional countries or sites may be added if necessary.

Sites that do not enroll subjects into an open cohort within 2 months of site initiation may be closed or replaced.

3.3 Number of Subjects

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

Approximately 78 subjects are planned for enrollment into this study. Approximately 39 subjects will be enrolled in the dose-escalation cohorts and approximately 39 subjects will be enrolled in the dose-expansion cohort of the study.

Based on emerging data, additional subjects may be enrolled.

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

3.4 Replacement of Subjects

A replacement subject who will be assigned to the same dose level may be enrolled if a subject is not DLT-evaluable in the dose-escalation cohorts. A DLT-evaluable subject is defined as receiving at least 90% of the planned doses of investigational product. Subjects in the dose-expansion cohort may be replaced if they discontinue from the study for reasons other than disease progression or toxicity.

3.5 Estimated Study Duration

The duration of this study will last approximately 2.5 years, with about 23 months for enrollment and 6 months protocol treatment period.

3.5.1 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for approximately 8 months including a screening period lasting 21 days, a treatment period lasting approximately 4 to 6 months, and a safety follow-up period lasting approximately 4 weeks. The actual duration for individual subjects will vary depending upon tolerability of AMG 211, evidence of clinical progression, and willingness to participate in the study.

In the event that a subject demonstrates clinical benefit from therapy, he or she may continue treatment with AMG 211 until he or she experiences an unacceptable adverse

event, confirmed disease progression per modified irRC (Appendix D), or he or she wishes to withdraw consent. Due to the mechanism of action of immune-enhancing therapies, subjects may experience infiltration of T cells in existing lesions leading to an apparent enlargement of existing lesions or the appearance of new lesions prior to maximal clinical benefit of AMG 211. The decision to continue on the study should be made by the treating physician and the subject.

End of study (EOS) for an individual subject is defined as the date of the final study visit (EOS visit) when safety assessments and procedures are performed. The EOS visit should occur approximately 4 weeks (+ 1 week) after the last dose of AMG 211 or at the initiation of other therapy. Subjects who complete the EOS visit will be considered to have completed the study.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis; the primary analysis for this study will occur after all dose-escalation cohort subjects and dose-expansion cohort subjects have completed 6 months of treatment or have discontinued treatment with AMG 211.

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study; the final analysis will occur at this time.

4. SUBJECT ELIGIBILITY

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

4.1 Inclusion Criteria

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

4.1.2 Male or Female ≥ 18 years of age at the time of informed consent

4.1.3 Pathologically documented, diagnosed GI adenocarcinoma (including but not limited to esophageal, gastric, small intestine, colorectal, or pancreatic cancers) that has failed standard treatments or for which standard curative or palliative measures do not exist or are no longer effective

4.1.4 At least 1 measurable tumor lesion per modified irRC (Appendix D)

4.1.5 Archival tumor tissue available or is willing to undergo biopsy of a tumor lesion before the start of treatment

4.1.6 Adequate hematological, renal, and liver function as follows:

- Absolute neutrophil count (ANC) > 1500/mm^3 (1.5×10^9/L)
- Platelet count > 100,000 mm^3 (100×10^9/L)
- White blood cell (WBC) count > 3×10^9/L
- Hemoglobin > 9.0 g/dL
- AST and ALT < 3.0 × the upper limit of normal (ULN)
- Alkaline phosphatase (ALP) ≤ 2.5 × ULN
- Total bilirubin (TBL) < 1.5 × ULN (unless subject has suspected Gilbert's syndrome or extrahepatic cause by increased indirect bilirubin fraction)
- Creatinine clearance > 50 mL/min calculated by Cockroft-Gault
- Lipase/amylase < 1.5 × ULN
- Prothrombin time, partial thromboplastin time, and international normalized ratio (INR) ≤ 1.5 × ULN

4.1.7 Life expectancy ≥ 3 months, in the opinion of the investigator

4.1.8 Karnofsky Performance Status ≥ 70%

4.1.9 Body weight ≥ 45 kg

4.2 Exclusion Criteria

4.2.1 History of allergy or reaction to any component of the AMG 211 formulation

4.2.2 Malignancy other than GI adenocarcinoma requiring current therapy

4.2.3 Evidence of uncontrolled systemic disease (other than GI adenocarcinoma)

4.2.4 Active infection or prior use of IV antibiotics for treatment of infection within 2 weeks prior to starting therapy with AMG 211

4.2.5 Corrected QT interval (QTc) ≥ 500 milliseconds at screening

4.2.6 Hepatitis B and/or C based on the following results:

- Positive Hepatitis B Surface Antigen (HepBsAg) (indicative of chronic Hepatitis B or recent acute Hepatitis B)
- Negative HepBsAg and positive Hepatitis B core antibody: Hepatitis B virus DNA by polymerase chain reaction (PCR) is necessary. Detectable Hepatitis B virus DNA suggests occult Hepatitis B.
- Positive Hepatitis C virus antibody (HepCAb) Hepatitis C virus RNA by PCR is necessary. Detectable Hepatitis C virus RNA suggests chronic Hepatitis C

4.2.7 Positive results for human immunodeficiency virus (HIV)

4.2.8 Major surgery within 28 days of study day 1

4.2.9 Prophylactic anti-infection vaccination within 1 month prior to starting therapy with AMG 211. Therapeutic vaccination for cancer or infection within 3 months prior to starting therapy with AMG 211.

4.2.10 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment in another investigational device or drug study. Other investigational procedures while participating in this study are excluded. Exception to this criterion is the participation in the Imaging Study and all procedures related to this study.

4.2.11 Treatment with any chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer within 14 days prior to study entry **or** not recovered from treatment

4.2.12 Unresolved toxicities from prior anti-tumor therapy, defined as not having resolved to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 grade 1 or to levels dictated in the eligibility criteria with the exception of alopecia or toxicities from anti-tumor therapy that are considered irreversible (defined as having been present and stable for > 6 months), may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and the sponsor

4.2.13 Recent history of cardiac disease, including myocardial infarction, unstable angina pectoris, or uncontrolled arrhythmia within 6 months; or evidence of severe congestive heart failure with New York Heart Association (Appendix G) severity classification > Class I within 12 weeks prior to screening

4.2.14 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above), that in the opinion of the investigator or sponsor would pose a risk to subject's safety or interfere with the study evaluation, procedures, or completion

4.2.15 Clinical history of significant central nervous system (CNS) pathology (including but not limited to: history of brain metastasis, multiple occurrences of confusion, dementia, previous CNS infarctions, migraine headaches [within 6 months prior to starting therapy with AMG 211], seizure disorder, or major brain surgery)

4.2.16 History of chronic autoimmune disease, eg, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, or multiple sclerosis (with the exception of stable type 1 diabetes)

4.2.17 Males or Females of reproductive potential and unwilling to practice an acceptable method of effective birth control while on study through 30 days after receiving the last dose of study drug. Acceptable methods of effective birth control include:

- sexual abstinence (males, females)
- use of a combination of 2 acceptable methods of effective birth control including: bilateral tubal ligation (females), vasectomy (males), oral, transdermal, injected, or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, contraceptive sponge with spermicide, cervical cap, or use of a condom with spermicide by the sexual partner)

4.2.18 Females who are lactating/breastfeeding or who plan to breastfeed while on study through 30 days after receiving the last dose of study drug

4.2.19 Females with a positive pregnancy test

4.2.20 Females planning to become pregnant while on study through 30 days after receiving the last dose of investigational product

4.2.21 Subject is likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study-specific activities/procedures. After meeting all eligibility criteria, a subject is considered enrolled on day 1 (cycle 1 day 1) when the cIV infusion with investigational product is started. The investigator is to document this decision and date in the subject's medical record and in/on the enrollment electronic case report form (eCRF). Adverse events are to be collected for an eligible subject once they are enrolled in the study (from cycle 1 day 1 onwards). Adverse Events occurring during the screening period and which are not related to study procedures will be captured as medical history.

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

The 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.

All screening tests and procedures should be performed within 21 days before enrollment, unless otherwise noted. All blood and urine samples collected for the

screening assessment (except for biomarkers and soluble CEA [sCEA]) will be submitted and analyzed by the local laboratory. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation (up to a total of 2 times during the screening period), if necessary before the subject is considered a screen failure.

Subjects who do not meet the eligibility criteria within the 21-day screening period will not be eligible for enrollment. Subjects may be re-screened up to 3 times at the discretion of the investigator. The subject must be re-consented if a re-screening attempt occurs outside the screening period. Subjects who are deemed not eligible will be documented as screen failures.

Subjects may be eligible to enroll once all screening tests and procedures are completed and results indicate that all eligibility criteria are met. A site representative will complete and send the enrollment eligibility worksheet to the sponsor or designee along with the lab results and any requested supporting documentation for review of eligibility criteria. The Amgen representative will acknowledge receipt of the paperwork and send confirmation of cohort and dose level assignment for the subject.

5.1 Treatment Assignment

An Amgen representative will notify the site(s) in writing when a cohort is open to screen new subjects. In the dose-escalation cohorts, subjects will be assigned sequentially into cohorts as they open. Three subjects will initially be enrolled into each dose-escalation cohort with at least a 48-hour interval between treatment start of subject 1 and subject 2 of each cohort. In the event that a DLT is observed, 3 additional subjects may be enrolled for a total of up to 6 evaluable subjects. Subjects are considered evaluable, for the purposes of the dose level review of safety information if they receive at least 90% of the planned doses of investigational product or if they have discontinued investigational product due to a DLT. Subsequent cohorts will begin enrollment upon completion of the previous cohort if it is deemed safe to proceed to the next dose level.

Subjects not participating in the Imaging Study will start enrollment into the dose-expansion cohort upon completion of the dose-escalation cohorts. Subjects concurrently participating in the Imaging Study will start enrollment into the dose-expansion cohort while dose-escalation cohorts are still open for enrollment.

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

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Products used in this study includes AMG 211 and IV bag protectant.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of AMG 211.

The medical devices used in this study include: portable infusion pump, IV bag, and infusion line including a 0.2 µm in-line filter.

6.2 Investigational Product

All investigational products will be dispensed at the research facility by a qualified staff member.

A physician or nurse trained in emergency medicine must be available when the infusion of investigational product is started for immediate intervention in case of complications.

6.2.1 Amgen Investigational Product AMG 211 and IV Bag Protectant

AMG 211 and the IV bag protectant will be manufactured by MedImmune Pharma BV, packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. AMG 211 will be presented as a sterile, single-use, lyophilized formulation for cIV infusion in a 3 mL glass vial containing 0.37 mg AMG 211. The formulation after reconstitution is 0.5 mg/mL in [redacted] mM sodium citrate/citric acid, [redacted] mM L-lysine hydrochloride, [redacted] mM ([redacted]% w/v) trehalose dihydrate, [redacted]% (w/v) polysorbate-80 at pH [redacted].

The IV bag protectant will be presented as a sterile liquid in a 20 **mm** glass vial **(containing 10 mL of IV bag protectant)** intended for pre-treatment of IV bags prior to dilution of AMG 211 drug product. The IV bag protectant does not contain an active pharmaceutical ingredient.

6.2.1.1 Dosage, Administration, and Schedule

AMG 211 will be delivered using preprogrammed infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 211 infusion for solution will be prepared in bags for IV infusion. The investigational product will be administered as a cIV infusion at a constant flow rate over 1 to 4 weeks followed by a 3-week (cohort 1 in the dose-escalation cohorts) or 2-week

(all other cohorts) treatment free interval prior to the following treatment cycle. Subjects will be hospitalized on day 1 cycle 1 for a minimum of 72 hours and at all subsequent cycles for a minimum of 48 hours. Subjects can be hospitalized for a longer time period at the discretion of the investigator. If required for logistical reasons (eg, long travel times), subjects may be hospitalized the day before dosing (day -1) of any cycle and at the EOI for cycle 1 for required PK samples. Subjects in the 7- and 14-day schedules will receive AMG 211 for 7 or 14 days followed by 21 days off or 14 days off, respectively (a 28-day cycle). Subjects on a 28-day schedule will receive AMG 211 for 28 days followed by 14 days off (a 42-day cycle).

The planned dose levels for the dose-escalation cohorts are: 200, 400, 800, 1600, 3200, and 6400 µg/d. Alternative dose levels up to 12800 µg/day will be explored in either 14-day or 28-day schedule based on emerging data. The MTD or recommended phase 2 dose will be administered in the dose-expansion cohort.

The infusion start time should be chosen carefully to avoid any interference or inconvenience with time points of safety assessments, PK/PD measurements, and infusion bag changes. The site should record any unscheduled interruption of an infusion on the eCRF, and provide the start and stop date/time of the infusion and the bag change.

AMG 211 should be administered through a central venous access. In the event that administration through a central venous access is not possible, AMG 211 may be administered temporarily through a peripheral venous line if the subject is hospitalized. The final solution for infusion should be administered through a 0.2 µm in-line filter.

Administration of the premedication (eg, dexamethasone) to minimize the risk of cytokine-release syndrome symptoms is recommended for all treatments at a dose of 800 µg/day or higher (see Section 6.5).

Infusion bags should be changed in accordance with local pharmacy standards for infusion of compounded sterile products up to every 4 days.

After completion of a first cycle without a DLT (may be 2 cycles in cohort 1), additional treatment cycles can be administered as long as in the judgment of the investigator the subject is deriving benefit.

Longer breaks of up to 8 weeks between treatment cycles will be allowed for subjects who remain on study treatment beyond 24 weeks from start of study treatment or in the event of urgent reasons other than adverse events related to study drug. The break

must be agreed upon after consultation with the sponsor and may be done to allow sufficient recovery from adverse events, due to the subject's schedule (eg, going on vacation) or for other reasons requiring a longer break.

The amount of investigational product used in preparation, total volume of preparation, concentration of preparation, quantity, dose, start date/time, stop date/time, and lot number of investigational product are to be recorded on each subject's eCRF.

The effects of overdose of this product are not known.

6.2.1.2 AMG 211 Outpatient Dosing

If deemed stable by the investigator, a subject may continue AMG 211 cIV infusion as an outpatient. In the outpatient setting, the subject will either return to the study site for infusion bag changes or the subject will be visited by a well-trained ambulant/home care service provider at specific intervals to change the infusion bag, **measure vital signs,** monitor and document adverse events and/or serious adverse events, and document any issues with the cIV infusion or infusion pump. The subject and ambulant/home care service provider will be trained and will receive written instructions for storage of the IV bags. The ambulant/home care service provider will complete source documentation before any study-related tasks are started.

In addition to visits, the ambulant/home care service provider **or study site personnel** will also contact the subject by telephone to monitor and document adverse events and/or serious adverse events and to document any issues with the cIV infusion or infusion pump. During cycle 1, the ambulant/home care service provider **or study site personnel** will contact the subject on each day that the subject is not hospitalized. Starting with cycle 2, the ambulant/home care service provider **or study site personnel** will contact the subject every 2 days except on those days that the subject will be visited to change the infusion bag.

Refer to the home health care manual for detailed information on the storage, handling, and administration of AMG 211, mandatory procedures, and data collection requirements.

Following each visit or telephone contact, the information collected will be documented on the Ambulant/Home Care Services visit worksheet and forwarded to the investigator. Any unexpected or unusual events as well as any deviations will be communicated promptly to the investigator. If any adverse event occurs in the outpatient setting, the ambulant/home care service provider should directly contact the site for further

management. The ambulant/home care service professionals provide 24 hour emergency on-call service. In the event of an interruption of the AMG 211 cIV infusion of > 24 hours, the restart of the infusion should be performed in the clinic/hospital under the supervision of the investigator or designee. Prophylactic treatment with steroid (eg, dexamethasone) is recommended before restarting of AMG 211 if clinically indicated.

6.2.1.3 Dose-cohort Study Escalation and Stopping Rules Dose-limiting Toxicities (DLT)

A DLT will be defined as any of the following occurring in a subject during the first 28 days of treatment and regarded by the investigators and/or sponsor to be related to AMG 211. The Common Terminology Criteria for Adverse Events (**CTCAE version 4.03**) will be used to assess toxicities/adverse events.

Hematological DLTs

- ANC < 0.5×10^9/L for ≥ 7 days
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with ANC < 0.5×10^9/L and fever ≥ 38.5°C
- Platelets < 25×10^9/L ≥ 7 days

Non-hematological DLTs

Any AMG 211-related ≥ grade 3 non-hematological toxicity **excluding**

- Nausea and vomiting, which is not refractory to anti-emetics
- Flare-up of pain because of potential increase in tumor volume is not regarded as a DLT
- Cytokine release syndrome manageable with symptomatic treatment and/or infusion interruption of up to 2 days

Subjects are evaluable for a DLT when they have received at least 90% of the planned doses of investigational product within the first treatment cycle (first 28 days of a cycle independent of length of the infusion) with or without the occurrence of a DLT in the 28-day safety observation period.

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

For certain toxicities such as laboratory abnormalities without a clear clinical correlation (eg, increase in serum lipase level without signs or symptoms of a clinical pancreatitis), a

discussion between the investigator and the sponsor may take place whether that adverse event should be assessed as a DLT.

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

6.2.1.4.1 Dose Reduction

Hematological criteria for dose reduction are presented in Table 4 and non-hematological criteria are presented in Table 5. Dose reduction is possible with re-treatment at 1 dose level lower (Table 5)

Table 4. Hematological Criteria for Dose Reduction

CTCAE Grade	ANC (10^9/L)	Platelets	Dose Delay[a]	Dose Reduction
Hematological				
0-2	> 1.0	> 50	Continue infusion	No change
3	< 1.0 – 0.5	< 50 – 25	Continue infusion until Investigator assesses toxicity to require interruption	No change
4	< 0.5	< 25	Delay until ≤ grade 2	Restart at 1 dose level lower

Table 5. Non-hematological Criteria for Dose Reduction

CTCAE Grade	Dose Delay	Dose Reduction	Comment
Non-hematological			
Infection, cytokine release syndrome, tumor lysis syndrome, diarrhea, hypoxia			
2	Delay until ≤ grade 1	No change	Restart in hospital
3	Delay until ≤ grade 1	Restart at 1 dose level lower	Consider re-escalation if completely recovered and no new toxicity occurred within 7 days of infusion. Permanent discontinuation of study treatment if no recovery within 21 days. Start at the same dose if resolved cytokine release syndrome, infection, tumor lysis syndrome, or hypoxia.
4	Discontinue infusion	Permanent discontinuation of study treatment	-
All other non-hematological toxicities and clinically significant laboratory parameters			
0-2	Continue infusion	No change	Interruption can be considered if deemed necessary by the investigator
3	Delay until ≤ grade 2	Resolution to grade 1 or 2: Restart at 1 dose level lower Resolution to normal within 1 week or a relationship to study drug can be ruled out: No change	Per the Investigator medical discretion to decide whether to continue the infusion for up to 72 hours if toxicity has not occurred during the DLT window and if the toxicity or abnormal labs are responding to treatment or represents an asymptomatic laboratory change. Permanent discontinuation of study treatment if no recovery within 21 days
4	Discontinue infusion	Permanent discontinuation of study treatment	-

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity

[a] Applies to all hematologic toxicity that persists for > 24 hours despite appropriate treatment

6.2.1.4.2 Infusion Interruption

Significant events requiring a change in treatment will be managed by immediate infusion interruption of equal or less than 24 hours. Both, infusion interruptions and treatment interruptions greater than 24 hours, have to be documented in the eCRF:

- The subject experiences a DLT as defined in Section 6.2.1.3
- The subject meets criteria for temporary or permanent discontinuation of investigational product as described in Section 8.3
- Technical problem with the infusion pump
- The investigational product is incorrectly prepared or administered (eg, overdose)

6.2.1.4.3 Restarting the Infusion

Treatment may resume if the interruption is ≤21 days and if:

- The interruption occurred due to other reasons than toxicity (technical or logistic reasons; eg, diagnostic measurements). The infusion can be restarted at the same dose and without additional measures.
- The toxicity has resolved to ≤ grade 1. The infusion can be restarted according to guidelines presented in Table 4 or Table 5.
- The toxicity occurred during the DLT period or has resolved to grade 2. The infusion can only be restarted in an individual subject with a clear clinical benefit from treatment after consultation with the sponsor on a case-by-case basis.

Restarting the infusion after a treatment interruption requires care. The start should be performed in the hospital with all infusion day 1 specific measures if the reason for the interruption was other than a technical issue or the interruption was > 24 hours independent of reason. Prophylactic treatment with steroid (eg, dexamethasone) is recommended before restarting of AMG 211 if clinically indicated.

Subjects that have had a treatment interruption during cycle 1 should be given the opportunity to complete a total of 14 or 28 days of infusion even though these may not be DLT evaluable subjects.

Subjects that have had a treatment interruption lasting ≥ 48 hours from cycle 2 onwards should re-start treatment as a new cycle.

6.2.1.4.4 Permanent Discontinuation

A subject will permanently discontinue treatment with investigational product in the event of:

- Dose-limiting or other unmanageable toxicity. If a DLT occurs in a subject with a clear clinical benefit from treatment a restart at a lower dose can be considered if the toxicity has resolved and after consultation with the sponsor.

- Disease progression documented on 2 consecutive imaging assessments separated by at least 4 weeks as defined by modified irRC (Appendix D). Subjects who show disease progression on a single imaging assessment and who show global clinical deterioration suggesting that no further benefit from treatment is likely should be discontinued from study treatment.
- Withdrawal of subject's consent
- Subject or investigator not compliant with the study protocol
- Occurrence or progression of a medical condition which in the opinion of the investigator should preclude further participation of the subject in the study

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

In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the EOIP and EOS visits. These data should be recorded, as they comprise an essential evaluation that should be performed prior to discharging any subject from the study and to allow for the evaluation of the study endpoints.

6.3 Other Protocol-required Therapies

All other protocol required therapies including corticosteroids, that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies. Please also refer to Section 6.5: Concomitant therapy.

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, ALP, AST, ALT, TBL) and/or 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.

6.4.1 Criteria for Permanent Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

Investigational product should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if ALL of the criteria below are met:

- TBL > 2 × ULN or INR > 1.5
- AND increased AST or ALT from the relevant baseline value as specified below:
  - Baseline AST or ALT value: < ULN
  - AST or ALT elevation: > 3 × ULN
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:
  - Hepatobiliary tract disease
  - Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, toxoplasmosis, and Parvovirus)
  - Right sided heart failure, hypotension, or any cause of hypoxia to the liver causing ischemia
  - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
  - Alpha-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomyolysis, hemolysis)

  If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen IP and other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.4.2 Criteria for Conditional Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational product outlined above and have no underlying liver disease, and

eligibility criteria requiring normal transaminases and TBL at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of Amgen investigational product and other protocol required therapies:

- Elevation of either AST or ALT according to the following schedule:
  - Baseline AST or ALT value: Any AST or ALT elevation: > 8 × ULN at any time
  - Baseline AST or ALT value: Any AST or ALT elevation: > 5 × ULN but < 8 × ULN for ≥ 2 weeks
  - Baseline AST or ALT value: Any AST or ALT elevation: > 5 × ULN but < 8 × ULN and unable to adhere to enhanced monitoring schedule
  - Baseline AST or ALT value: Any AST or ALT elevation: > 3 × ULN with clinical signs or symptoms which are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, or jaundice).
- OR: TBL > 3 × ULN at any time
- OR: ALP > 8 × ULN at any time

AMG 211 should be withheld pending investigation into alternative causes of DILI. If the investigational product is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

6.4.3 Criteria for Rechallenge of Amgen Investigational Product After Potential Hepatotoxicity

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

If signs or symptoms recur with rechallenge, then the investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.1.4.4) should never be rechallenged.

6.5 Concomitant Therapy

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

Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

Concomitant therapies are to be collected from informed consent, through the EOS. For

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

Oxygen administration as supportive measure is permitted during study treatment.

For symptomatic treatment of fever > 38.5°C metamizole as infusion and/or paracetamol, ibuprofen, or acetylsalicylic acid are recommended.

Patients should be closely monitored for any signs and symptoms that may be associated with CRS such as pyrexia, headache, nausea, vomiting, asthenia, hypotension, hypoxia and tachycardia during the initiation of AMG 211 treatment. To mitigate the CRS risk prophylactic treatment with steroids (dexamethasone) is recommended to be administered before the first dose (initial cycle) of AMG 211, and before subsequent cycles of AMG 211 (if clinically indicated). **In the event of CRS, an unscheduled blood sample should be collected to measure cytokine levels.**

- The sponsor may recommend treating subjects with prophylactic dexamethasone according to the following: Dexamethasone at a dose of 8 mg or equivalent corticosteroid will be administered
  - 8 to 12 hours prior to the start of the infusion on day -1
  - 1 hour prior to the start of the infusion on day 1
  - Every 8 to 12 hours after start of infusion on days 1 and 2
- Corticosteroid treatment can be continued if deemed necessary by the investigator and after consultation with the sponsor but doses should be tapered as quickly as feasible. Further variations may be needed that should be discussed and agreed upon in a Dose Level Review Meeting (DLRM).

6.6 Medical Devices

The investigational product must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment in both the inpatient and outpatient setting. Investigational product infusion for solution will be prepared in bags for IV infusion and delivered through infusion lines with a 0.2 µm in-line filter that are both compatible with the investigational product as described in the IPIM.

Additional details for the use of the above mentioned medical devices and specific set of device specifications are provided in the IPIM.

Additional medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not provided or reimbursed by Amgen (except, if required by local regulation). The investigator overseeing the conduct of the study at each respective institution will be responsible for obtaining these supplies.

6.7 Excluded Treatments and/or Procedures During Study Period

Any anti-tumor therapy other than the investigational product, including cytotoxic and/or cytostatic drugs, hormonal therapy, immunotherapy or any biological response modifiers, any other investigational agent, chronic systemic corticosteroid therapy, other immunosuppressive therapies, or stem-cell transplantation is not allowed.

Radiotherapy is not permitted except for palliation of symptoms and should be discussed with the sponsor's Medical Monitor first. Investigators should ensure that the need for radiation does not indicate progressive disease and that for subjects with measurable disease, radiation is not to the sole site of measurable disease.

The following procedures should also not be undertaken within the timeframes specified prior to enrollment and during the study:

- Participation in an investigational study (drug or device) within 28 days of study day 1. Exception to this criterion is the participation in the optional Imaging Study and all procedures related to this study.
- Major surgery within 28 days of study day 1
- Enrollment into another investigational drug or device study with the exception of participation in the Imaging Study.

6.8 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 any investigational or non-investigational product(s) or device(s).

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

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 6. Schedule of Assessments - Cohort 1 (7-day Infusion Cycle 1 and 14-day Infusion for all Subsequent Cycles)

	SCR	Treatment Period																												
Cycle		1																		2 and all subsequent cycles [k]								Q2C	EOIP	
Study Day	-14 to -1	1									2	3-5	8					9	15	22	1			2	3-5	8	15	22			
Hours		Pre-dose	Relative to start of infusion: 0-1.5	2	3	4	6	8	12	14	20	24	48-96	Relative to EOI: EOI	0.5	2	4	8	24			Pre-dose	Relative to start of infusion: 0	6	24	48-96	168	336				
GENERAL ASSESSMENTS																														
Informed consent	X																													
Hospitalization							X[c]															X[c]								
Concomitant medications	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Adverse events	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	X
Clinical evaluation[a]	X	X									X	X	X					X	X	X	X			X	X	X	X	X		X	X
Vital signs, pulse oximetry	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X					X	X	X	X		X[i]	X	X	X	X	X		X	X
12-lead ECG (triplicate measurement)	X	X									X		X							X	X[e]			X[e]			X[e]			X
LABORATORY ASSESSMENTS																														
Serum pregnancy test[h]	X	X																			X									
Coagulation	X	X									X	X	X						X	X	X			X	X		X	X		X	X
Hematology, Chemistry	X	X									X	X	X						X	X	X			X	X		X	X		X	X
Urinalysis	X	X									X	X	X						X	X	X			X	X		X	X		X	X
Hepatitis serology, HIV	X																													
Anti-AMG 211-antibody		X																X										X		X	X
DOSING																														
AMG 211			X																			X								
TUMOR ASSESSMENTS																														
MRI or CT	X[g]																											X[f]		X[f]
Tumor markers (eg, CEA)	X	X											X															X[f]	X	X
BIOMARKER ASSESSMENTS																														
Circulating tumor cells	X	X											X															X[f]	X	X
Immune cells	X	X					X				X	X	X								X[e]			X[e]	X[e]	X[e]	X[e]		X	X
Soluble DNA markers	X	X		X			X				X	X	X								X[e]			X[e]	X[e]	X[e]	X[e]		X[f]	X	X
Serum markers		X					X				X	X	X								X[e]			X[e]	X[e]	X[e]					
Archival tumor tissue	X																														
Tumor biopsy[b]	X																														
PK ASSESSMENTS																														
AMG 211 PK collection		X		X			X				X	X	X	X	X	X	X	X						X[e]	X[e]		X[e]				
sCEA	X	X		X			X				X	X	X											X[e]	X[e]		X[e]				

Footnote defined on next page

CT = computed tomography; EOI = End of Infusion; EOS = End of Study; EOIP = End of Investigational Product; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irRC = immune-related response criteria; MRI = magnetic resonance imaging; Q2C = Every 2 cycles SCR = Screening

[a] Clinical evaluations will include physical examination, Karnofsky Performance Status, and weight. Screening only: medical history and height will also be obtained.

[b] Core biopsy is optional at screening if an Archived Tumor Tissue sample is available. If a core biopsy is performed, it must be completed before the start of treatment.

[c] Hospitalization for cycle 1 will be for a minimum of 72 hours. Hospitalization for all subsequent cycles will be for a minimum of 48 hours.

[d] Vital signs and pulse oximetry will be taken every 30 minutes.

[e] Obtained at cycle 2 only.

[f] Every 2 cycles (8 to 10 weeks for 4-week cycle) post-therapy initiation. The **MRI or CT** can be obtained earlier if clinical deterioration necessitates an earlier scan. Using the **MRI or CT**, disease will be assessed using the modified irRC. **Both** response (irCR, irPR) and progression (irPD) require confirmation by a repeat, consecutive assessment at least 4 weeks from the date of the first documented assessment, **and the timing of the scan is a medical decision of the managing physician considering the clinical condition of the subject and other laboratory findings**. The confirmatory scan can also be performed at the next scheduled imaging visit **if confirming response**.

[g] Tumor evaluation by contrast-enhanced **MRI or CT** of the chest, abdomen, and pelvis will be performed during screening (within 28 days of cycle 1 day 1). Using the **MRI or CT**, disease will be assessed using the modified irRC.

[h] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[i] **Vital signs and pulse oximetry will be taken every 6 hours.**

[j] Radiographic assessment at the end of the study or during the follow-up visits should be performed if the last imaging assessment was performed ≥ 6 weeks before the EOS and the subject has not had evidence of confirmed disease progression.

[k] Start of treatment at cycle 2 and all subsequent cycles can start +1 day if justified logistical reasons (eg, bank holiday)

Table 7. Schedule of Assessments - Cohorts 2 to 7 (14-day Infusion for all Cycles)

	SCR	Treatment Period																														
Cycle		1																	2 and all subsequent cycles[k]								Q2C	EOIP	
Study Day	-21 to - 1	1									2	3-5	8	11	15					16	22	1		2	3-5	8	15	22			
Hours		Pre-dose	Relative to start of infusion												Relative to EOI							Pre-dose	Relative to start of infusion									
			0-1.5	2	3	4	6	8	12	14	20	24	48-96	168		EOI	0.5	2	4	8	24			0	6	24	48-96	168	336				EOS
GENERAL ASSESSMENTS																																
Informed consent	X																															
Hospitalization			X[c]																			X[c]										
Concomitant medications	X	X	→																											X	X	
Adverse events	X	X	→																											X	X	
Clinical evaluation[a]	X	X									X	X	X	X	X					X	X	X			X	X	X	X	X		X	X
Vital signs, pulse oximetry	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		X[f]	X	X	X	X	X		X	X
12-lead ECG (triplicate measurement)	X	X									X				X						X	X[e]			X[e]				X[e]			X
LABORATORY ASSESSMENTS																																
Serum pregnancy test[h]	X	X																				X										
Coagulation	X	X									X	X	X	X	X						X	X			X	X		X	X		X	X
Hematology, Chemistry	X	X									X	X	X	X	X						X	X			X	X		X	X		X	X
Urinalysis	X	X									X	X	X	X	X						X	X			X	X		X	X		X	X
Hepatitis serology, HIV	X																															
Anti-AMG 211-antibody		X																		X									X		X	X
DOSING																																
AMG 211			X																			X										
TUMOR ASSESSMENTS																																
MRI or CT	X[g]																													X[f]		X[j]
Tumor markers (eg, CEA)	X	X																		X		X						X			X	X
BIOMARKER ASSESSMENTS																																
Circulating tumor cells	X	X													X															X[f]	X	X
Immune cells	X	X					X				X	X	X		X							X[e]			X[e]	X[e]	X[e]	X[e]			X	X
Soluble DNA markers	X	X		X			X				X	X	X		X							X[e]			X[e]	X[e]	X[e]	X[e]		X[f]	X	X
Serum markers		X					X				X	X	X									X[e]			X[e]	X[e]	X[e]					
Archival tumor tissue	X																															
Tumor biopsy[b]	X												X[l]														X[l]					
PK ASSESSMENTS																																
AMG 211 PK collection		X		X			X				X	X	X		X	X	X	X	X	X					X[e]	X[e]		X[e]				
sCEA	X	X		X			X				X	X	X		X										X[e]	X[e]		X[e]				

Footnote defined on next page

CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; EOI = End of Infusion; EOS = End of Study; EOIP = End of Investigational Product; HIV = human immunodeficiency virus; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irRC = immune-related response criteria; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q2C = Every 2 cycles; sCEA = soluble carcinoembryonic antigen; SCR = Screening

[a] Clinical evaluations will include physical examination, Karnofsky Performance Status, and weight. Screening only: medical history and height will also be obtained.

[b] Core biopsy is optional at screening if an Archived Tumor Tissue sample is available. If a core biopsy is performed, it must be completed before the start of treatment. Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8 to 14) and/or an optional on-treatment biopsy at cycle 1 day 8 to 14.

[c] Hospitalization for cycle 1 will be for a minimum of 72 hours. Hospitalization for all subsequent cycles will be for a minimum of 48 hours.

[d] Vital signs and pulse oximetry will be taken every 30 minutes.

[e] Obtained at cycle 2, 4, 6 and 8 only.

[f] Every 2 cycles (8 to 10 weeks for 4-week cycle) post-therapy initiation. The **MRI or CT** can be obtained earlier if clinical deterioration necessitates an earlier scan. Using the **MRI or CT**, disease will be assessed using the modified irRC. **Both** response (irCR, irPR) and progression (irPD) require confirmation by a repeat, consecutive assessment at least 4 weeks from the date of the first documented assessment, **and the timing of the scan is a medical decision of the managing physician considering the clinical condition of the subject and other laboratory findings**. The confirmatory scan can also be performed at the next scheduled imaging visit **if confirming response**.

[g] Tumor evaluation by contrast-enhanced **MRI or CT** of the chest, abdomen, and pelvis will be performed during screening (within 28 days of cycle 1 day 1). Using the **MRI or CT**, disease will be assessed using the modified irRC.

[h] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[i] **Vital signs and pulse oximetry will be taken every 6 hours.**

[j] Radiographic assessment at the end of the study or during the follow-up visits should be performed if the last imaging assessment was performed ≥ 6 weeks before the EOS and the subject has not had evidence of confirmed disease progression

[k] Start of treatment at cycle 2 and all subsequent cycles can start +1 day if justified logistical reasons (eg, bank holiday)

[l] One optional tumor biopsy may be provided at cycle 1 after the first or second week of treatment with AMG211, and a separate optional biopsy may be provided at cycle 2 or a subsequent cycle after the first or second week of treatment with AMG211.

Table 8. Schedule of Assessments – 28-day Infusion for all Cycles

	SCR	Treatment Period																																				
Cycle		1																										2 and all subsequent cycles[l]										
Study Day	-21 to -1	1										2	3-5	8	11	15	18	22	25	29					30	36	1			2	3-5	8	15	22	29	36		
Hours		Pre-dose	Relative to start of infusion																	Relative to EOI							Pre-dose	Relative to start of infusion									
			0-1.5	2	3	4	6	8	12	14	20	24	48-96	168						EOI	0.5	2	4	8	24			0	6	24	48-96	168	336					
GENERAL ASSESSMENTS																																						
Informed consent	X																																					
Hospitalization			X[c]																								X[c]											
Concomitant medications	X	X	→																																			
Adverse events	X	X	→																																			
Clinical evaluation[a]	X	X										X	X	X	X	X	X	X	X	X					X	X	X			X	X	X	X	X	X	X		
Vital signs, pulse oximetry	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		X[h]	X	X	X	X	X	X	X		
12-lead ECG (triplicate measurement)	X	X										X								X						X	X[e]			X[e]							X[e]	
LABORATORY ASSESSMENTS																																						
Serum pregnancy test[g]	X	X																									X											
Coagulation	X	X										X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X		
Hematology, Chemistry	X	X										X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X		
Urinalysis	X	X										X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X		
Hepatitis serology, HIV	X																																					
Anti-AMG 211-antibody		X																							X												X	
DOSING																																						
AMG 211			X																									X										
TUMOR ASSESSMENTS																																						
MRI or CT	X[f]																																					
Tumor markers (eg, CEA)	X	X																		X							X										X	
BIOMARKER ASSESSMENTS																																						
Circulating tumor cells	X	X														X				X																		
Immune cells	X	X					X					X	X	X		X		X		X							X[e]			X[e]	X[e]	X[e]	X[e]		X[e]		
Soluble DNA markers	X	X		X			X					X	X	X		X		X		X							X[e]			X[e]	X[e]	X[e]	X[e]				
Serum markers		X					X					X	X	X													X[e]			X[e]	X[e]	X[e]					
Archival tumor tissue	X																																					
Tumor biopsy[b]	X													X[k]																	X[k]						
PK ASSESSMENTS																																						
AMG 211 PK collection		X		X			X					X	X	X		X				X	X	X	X	X	X					X[e]	X[e]		X[e]		X[e]		
sCEA	X	X		X			X					X	X	X		X				X										X[e]	X[e]		X[e]		X[e]		

Footnote defined on next page

CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; EOI = End of Infusion; EOS = End of Study; EOIP = End of Investigational Product; HIV = human immunodeficiency virus; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irRC = immune-related response criteria; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q2C = Every 2 cycles; sCEA = soluble carcinoembryonic antigen; SCR = Screening

[a] Clinical evaluations will include physical examination, Karnofsky Performance Status, and weight. Screening only: medical history and height will also be obtained.

[b] Core biopsy is optional at screening if an Archived Tumor Tissue sample is available. If a core biopsy is performed, it must be completed before the start of treatment. Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8) and/or an optional on-treatment biopsy at cycle 1 day 8.

[c] Hospitalization for cycle 1 will be for a minimum of 72 hours. Hospitalization for all subsequent cycles will be for a minimum of 48 hours.

[d] Vital signs and pulse oximetry will be taken every 30 minutes.

[e] Obtained at cycle 2, 4, 6 and 8 only.

[f] Tumor evaluation by contrast-enhanced **MRI or CT** of the chest, abdomen, and pelvis will be performed during screening (within 28 days of cycle 1 day 1). Using the **MRI or CT**, disease will be assessed using the modified irRC.

[g] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[h] **Vital signs and pulse oximetry will be taken every 6 hours.**

[j] Start of treatment in cycle 2 and all subsequent cycles can start +1 day if justified logistical reasons (eg, bank holiday)

[k] One optional tumor biopsy may be provided at cycle 1 after the first or second week of treatment with AMG211, and a separate optional biopsy may be provided at cycle 2 or a subsequent cycle after the first or second week of treatment with AMG211.

Table 8. Schedule of Assessments – 28-day Infusion for all Cycles

	Treatment Period		
Cycle	**Q2C**	**EOIP**	**EOS**
Study Day			
Hours			
GENERAL ASSESSMENTS			
Informed consent			
Hospitalization			
Concomitant medications		X	X
Adverse events		X	X
Clinical evaluation[a]		X	X
Vital signs, pulse oximetry		X	X
12-lead ECG (triplicate measurement)			X
LABORATORY ASSESSMENTS			
Serum pregnancy test[g]			
Coagulation		X	X
Hematology, Chemistry		X	X
Urinalysis		X	X
Hepatitis serology, HIV			
Anti-AMG 211-antibody		X	X
DOSING			
AMG 211			
TUMOR ASSESSMENTS			
MRI or CT	**X**[i]		X[j]
Tumor markers (eg, CEA)		X	X
BIOMARKER ASSESSMENTS			
Circulating tumor cells	X[i]	X	X
Immune cells		X	X
Soluble DNA markers	X[i]	X	X
Serum markers			
Archival tumor tissue			
Tumor biopsy[b]			
PK ASSESSMENTS			
AMG 211 PK collection			
sCEA			

Page 2 of 2

Footnote defined on next page

CEA = carcinoembryonic antigen; CT = computed tomography; ECG = electrocardiogram; EOI = End of Infusion; EOS = End of Study; EOIP = End of Investigational Product; HIV = human immunodeficiency virus; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irRC = immune-related response criteria; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q2C = Every 2 cycles; sCEA = soluble carcinoembryonic antigen; SCR = Screening

[a] Clinical evaluations will include physical examination, Karnofsky Performance Status, and weight. Screening only: medical history and height will also be obtained.

[b] Core biopsy is optional at screening if an Archived Tumor Tissue sample is available. If a core biopsy is performed, it must be completed before the start of treatment. Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8 to 28) and/or an optional on-treatment biopsy at cycle 1 day 8 to 28.

[g] Serum pregnancy test will be performed for all females unless surgically sterile or $\geq$ 2 years postmenopausal.

[i] Every 2nd cycle (10 to 12 weeks for 6-week cycle) post-therapy initiation. The **MRI or CT** can be obtained earlier if clinical deterioration necessitates an earlier scan. Using the **MRI or CT**, disease will be assessed using the modified irRC. **Both** response (irCR, irPR) and progression (irPD) require confirmation by a repeat, consecutive assessment at least 4 weeks from the date of the first documented assessment, **and the timing of the scan is a medical decision of the managing physician considering the clinical condition of the subject and other laboratory findings**. The confirmatory scan can also be performed at the next scheduled imaging visit **if confirming response**.

[j] Radiographic assessment at the end of the study or during the follow-up visits should be performed if the last imaging assessment was performed ≥ 6 weeks before the EOS and the subject has not had evidence of confirmed disease progression

7.2 General Study Procedures

A signed and dated IRB/IEC approved ICF must be obtained prior to performing any study-specific procedures. All screening procedures must be performed within 21 days of enrollment, unless otherwise noted. Subjects who meet the inclusion and exclusion criteria will be eligible to be enrolled in the study. A subject may be rescreened up to 3 additional times during the study at the discretion of the investigator.

During the study, every effort should be made to perform the study procedures as indicated on the Schedules of Assessments (Table 6, Table 7, and Table 8). Subjects will be seen in the clinic for study evaluations. When electrocardiograms (ECGs), vital signs, blood sample collections, biomarker development sample collections, and biopsy sample collections occur on the same visit, ECGs and vital signs should be performed before samples (blood, biopsy) are collected. Blood samples must not be taken/drawn from the port catheter. The time of blood sample collection must be recorded with the exact time of collection (do not use the time that the samples were frozen or any other time point). If blood samples will be collected on the same day that the infusion bag is being changed, the blood samples must be collected before the infusion bag is changed.

The study specific manuals and Imaging Manual provide additional details regarding the requirements for these procedures.

Acceptable deviation windows are as follows:

- ECGs, biomarker blood draws, and PK blood draws: ± 15 minute window if collected within the first 24 hours after the start of an infusion or within the first 24 hours after the EOI.
- Subsequent cycles (beginning with cycle 2): ± 2-day window. PK samples in cycle 2 should be taken between 24 hours post start of infusion and before EOI.

Local laboratories should be used for the following assessments: hematology, clinical chemistry including tumor markers, coagulation, urinalysis, hepatitis serology, HIV, and serum pregnancy tests. The following collections will be shipped to a central laboratory for analysis: blood samples for determination of plasma concentrations of AMG 211, biomarker samples, biomarker development samples, and biopsy samples. Refer to the laboratory manual for detailed collection, processing, and shipping procedures.

7.2.1 Screening

After written informed consent has been obtained, subjects will be screened in order to assess eligibility for study participation. The total screening window is up to 21 days, unless otherwise noted. The screening period starts on the day that informed consent is obtained. If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen failure. Subjects who screen fail may be eligible to re-screen per the investigator's discretion. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation during each screening period before the subject is considered a screen failure. The subject must be re-consented if a re-screening attempt occurs outside the screening period.

The following procedures are to be completed during the screening period at the time points designated in the Schedules of Assessments (Table 6, Table 7, and Table 8).

- Confirmation that the ICF has been signed
- Demographic data including sex, date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety
- Clinical evaluation
  - Physical examination as per standard of care (including medical/surgical history). Physical examination findings should be recorded on the appropriate eCRF.
  - Karnofsky Performance Status
  - Height and weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, serum pregnancy test (females only), hepatitis serology, HIV, and tumor markers
- Biomarker assessments: CTCs, immune cells, **soluble DNA markers,** archival tumor tissue, core biopsy (if required)
- sCEA sample collection
- Imaging assessments (**magnetic resonance imaging [MRI]** or **computed tomography [CT])** within 28 days prior to study day 1
- Disease assessment based on modified irRC (Appendix D)
- Serious adverse event reporting
- Documentation of concomitant and rescue medications. All prior cancer treatment therapies will be collected, and other prior therapies that were being taken within 30 days preceding start of study treatment should be collected. For prior therapies, collect therapy name, indication, dose, unit, frequency, start date, and stop date.
- Collection of archived tumor tissue or new biopsy (imaging guided eg, ultrasound).

7.2.2 Treatment

Subjects will be hospitalized on day 1 of cycle 1 for a minimum of 72 hours and at all subsequent cycles for a minimum of 48 hours. Subjects can be hospitalized for a longer time period at the discretion of the investigator. If required for logistical reasons (eg, long travel times), subjects may be hospitalized the day before dosing (day -1) of any cycle and at the EOI for cycle 1 for required PK samples.

Subjects in the 7- and 14-day schedules will receive AMG 211 for 7 or 14 days followed by 21 days off or 14 days off, respectively (a 28-day cycle). Subjects on a 28-day schedule will receive AMG 211 for 28 days followed by 14 days off (a 42-day cycle).

Two visits per week will be scheduled during the ongoing infusion in cycle 1 (and cycle 2 in cohort 1) and weekly visits will be required for the remainder of the cycle following completion of the infusion. In subsequent treatment cycles, weekly visits will be required during treatment.

Treatment begins on day 1 (cycle 1 day 1) when the first cIV infusion of investigational product is administered to a subject.

The following procedures will be completed during the treatment period at the times designated in the Schedules of Assessments (Table 6, Table 7, and Table 8). Investigational product is to be administered after all other protocol-required pre-dose assessments have been performed during each visit that it is administered.

- Hospitalization
- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - Karnofsky Performance Status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, and serum pregnancy test (females only), and tumor markers
- Biomarker assessments: CTCs, immune cells, soluble DNA markers, serum markers, and core biopsy (if separate consent provided)
- AMG 211 PK and sCEA sample collection
- Anti-AMG 211 antibody sample collection
- Imaging assessments (**MRI or CT**)

- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications
- Receipt of protocol-required therapies

7.2.3 End of Investigational Product (EOIP)

The EOIP visit will occur upon documented confirmed clinical or radiographic disease progression, intolerable adverse event, or withdrawal of consent. For subjects who choose to discontinue investigational product treatment, the EOIP visit should occur as soon as possible after the last dose of investigational product is administered. Medically significant adverse events, considered related to the investigational product by the investigator or the sponsor, will be followed until resolved or considered stable. The following procedures will be completed during the EOIP visit as designated in the Schedules of Assessments (Table 6, Table 7, and Table 8).

- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - Karnofsky Performance Status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis
- Biomarker assessments: CTCs, immune cells, and soluble DNA markers
- Anti-AMG 211 antibody sample collection
- Tumor markers
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications

7.2.4 End of Study (EOS) Visit

The EOS visit is a safety follow-up visit that is to be performed at least 4 weeks (or up to 7 days thereafter) after the last dose of AMG 211. All efforts should be made to conduct this visit. If it is not possible to conduct the EOS visit, documentation of the efforts to complete the visit should be provided in the source documents and noted as not done in the eCRF.

The following procedures will be completed at the EOS visit as designated in the Schedules of Assessments (Table 6, Table 7, and Table 8).

- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - Karnofsky Performance Status
  - Weight
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis
- Biomarker assessments: CTCs, immune cells, and soluble DNA markers
- Anti-AMG 211 antibody sample collection
- Tumor markers
- Imaging assessments (MRI or CT) if last imaging assessment was performed ≥ 6 weeks before the EOS and the subject has not had evidence of confirmed disease progression
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications

7.3 Description of Study Procedures

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

7.3.1 Informed Consent

A signed ICF must be obtained from each subject prior to any study-mandated procedures.

7.3.2 Demographic Data

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

7.3.3 Medical History, Current Malignancy and Prior Therapy

The investigator or designee will collect a complete medical and surgical history that started 5 years prior to screening through the time of consent. Medical history will

include information on the subject's concurrent medical conditions. Record all findings on the Medical History eCRF or Current Malignancy eCRF as appropriate.

Relevant medical history, including previous chemotherapy or radiotherapy, antecedent hematologic or oncologic disease, other diseases/symptoms such as fatigue, bleeding, and infection (resolved and ongoing) will be collected. The history of GI adenocarcinoma must date back to the initial diagnosis and any response duration. The current toxicity grade will be collected for each condition that has not resolved.

7.3.4 Concomitant Medications

Concomitant therapies are to be collected from informed consent through the EOS. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.3.5 Clinical Evaluation

7.3.5.1 Physical Examination

A complete physical examination as per standard of care (rectal and vaginal examination not required) will be performed by the investigator or designee at screening and at the time points specified in the Schedules of Assessments (Table 6, Table 7, and Table 8). The physical examination will include general appearance, including examination of the skin, spleen, respiratory, cardiovascular, musculoskeletal, and neurological systems.

The individual performing the physical examination will characterize their findings as either normal or abnormal. Abnormal physical examination findings found during screening should be reported on the Medical History eCRF. Abnormal physical examination findings found after the subject has received investigational product will be reported on the Adverse Event eCRF.

7.3.5.2 Karnofsky Performance Status

Subjects will be graded according to the Karnofsky Performance Status.
See Appendix F.

7.3.5.3 Height Measurements

Height in centimeters should be measured without shoes at screening.

7.3.5.4 Weight Measurements

Weight in kilograms should be measured without shoes.

7.3.6 Radiological Assessment

Radiological imaging to assess the extent of disease will be assessed by standardized contrast-enhanced MRI or CT and evaluated according to modified irRC

(Wolchok JD et al, 2009; Appendix D). **A contrast-enhanced MRI should be the preferred imaging method for tumor staging. A CT should be done when MRI is not possible, is relatively contraindicated (eg, allergy to contrast) or for the evaluation of body sites where MRI is not the recommended adequate staging method. In order to reduce radiation exposure for subjects, low dose CT techniques should be applied whenever possible. Organ-specific imaging protocols or existing diagnostic guidelines should be followed whenever possible to evaluate the extent of the disease appropriately.** Radiographic imaging of the chest, abdomen, and pelvis are required at screening. Tumor assessments must also include all other sites of disease. The screening imaging studies must be performed within 28 days prior to study day 1 and will be used as baseline. During treatment, follow-up radiographic imaging of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, will be performed every 8 to 10 weeks post-therapy initiation in cohorts with 7- or 14-day infusions and every 10 to 12 weeks post-therapy initiation in cohorts with 28-day infusion unless clinical deterioration necessitates an earlier scan or disease progression has been confirmed as defined by modified irRC (Appendix D). Response (immune-related Complete Response [irCR], immune-related Partial Response [irPR]) and progression (immune-related Progressive Disease [irPD]) require confirmation by a repeat, consecutive assessment no less than 4 weeks from the date of the first documented assessment.

For confirming progression, the repeat scan may be performed any time after 4 weeks from the first suspected radiologic evidence of progression at the discretion of the managing physician considering the clinical condition of the subject and other laboratory findings.

For confirming response, the repeat scan may be performed any time after 4 weeks from the first suspected radiologic evidence of response and may be delayed until the next scheduled scan to avoid unnecessary procedures.

See also description in Table 6, Table 7, and Table 8.

Radiographic assessment at the end of the study or during the follow-up visits should be performed if the last imaging assessment was performed ≥ 6 weeks before the EOS and the subject has not had evidence of confirmed disease progression.

All scans for tumor response assessment will be done using criteria as indicated in the Imaging Manual provided by the core laboratory. All subsequent scans will be

performed in the same manner as at screening, preferably on the same scanner (unless a subject develops hypersensitivity to **MRI** contrast **or to the procedure** during the study, in which case a switch to **CT** is acceptable after consultation with Amgen and the imaging core laboratory).

Determination of disease response for clinical management of subjects will be assessed at the clinical sites per modified irRC. Scans will be submitted to the imaging core laboratory for response assessment using modified irRC and for exploratory analysis such as volumetric and non-necrotic tumor measurements. Detailed information regarding the submission of images to the core laboratory is found in the Imaging Manual.

7.3.7 Archived Tumor Tissue Samples

During screening, a block(s) of archived paraffin-embedded tumor tissue collected prior to the study will be sent to the central laboratory along with the corresponding pathology report. In lieu of a whole block, approximately 30 unstained sections on charged slides from the same block obtained in the 3 months before screening can be submitted to the central laboratory.

It is important that adequate tissue samples are sent to the central laboratory, within 4 weeks of enrollment to allow time to evaluate the samples, and to ask for additional samples if the initial samples are not appropriate. The tumor block should be carefully selected by a pathologist or a skilled experienced histology associate and should include a deep diagnostic section containing tumor tissue.

Tissue samples will be used to help identify genes and other markers that may enhance our understanding of the cancer and/or determine how subjects respond (positively or negatively) to the investigational product.

Refer to the laboratory manual for detailed collection and handling procedures for all tumor tissue samples.

7.3.8 Tumor Biopsy

To meet eligibility requirements, archived tumor tissue must be confirmed available during the screening period and if not available, the subject must consent to a biopsy procedure before the start of treatment. The decision to biopsy will be made once subject eligibility has been determined and on the basis of tumor accessibility and subject safety. Subjects must sign a separate consent to undergo a biopsy procedure.

Subjects in the 14-day or 28-day infusion cohorts may also provide a separate consent to undergo one or two optional on-treatment biopsies:

- One biopsy on cycle 1 after the first or second week of treatment with AMG211.
- One biopsy provided in cycle 2 or subsequent cycles after the first or second week of treatment with AMG 211.

Subjects in the 14-day or 28-day infusion cohorts who provide a separate consent may also undergo 2 optional tumor biopsies (paired biopsy). Subjects would undergo the first biopsy procedure within 2 weeks before the first dose of AMG 211 (cycle 1 day 1) and then the second biopsy (on-treatment) procedure would be performed on cycle 1 day 8 of the study drug infusion. The on-treatment biopsy should preferentially be collected on cycle 1 day 8 or within ± 2 days (between cycle 1 day 6 and cycle 1 day 10) or at the latest at the end of the treatment cycle.

Subjects must have more than 1 measurable lesion remaining for the on-treatment biopsy to allow for a response assessment after treatment.

The biopsy must be obtained imaging-guided (at least ultrasound-guidance should be used).

If subjects undergo a diagnostic or invasive intervention or surgery during the trial as per the investigator's discretion, subjects may consent to donate a portion of their tumor and or associated tissues (eg, malignant effusion) to this study.

The corresponding pathology report must be submitted for any biopsy provided for the study.

The comparison of pre- and on-treatment tumor tissue will inform tumor PK, tumor and T cell PD markers, and can be used to assess potential resistance mechanisms.

Eligible subjects who provide consent for a tumor biopsy must have tumor tissue that is accessible by core biopsy using minimally invasive procedures. The tumor tissue biopsied must be subcutaneous nodules, subcutaneous lymph nodes, or lesions that are accessible by core biopsy with or without CT or ultrasound guidance. Additionally, subjects with tumors in the upper GI tract (ie, accessible tumors in the esophagus) may undergo an endoscopic biopsy. Fine needle aspirate and colonoscopy can also be performed as long as it is accompanied by a core biopsy. Biopsy specimens will be obtained using standard surgical techniques or by percutaneous core needles.

Excisional biopsy following cycle 2 or later cycles is permissible.

7.3.9 Vital Signs

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

The 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 signs eCRF.

The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

7.3.10 Pulse Oximetry

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

7.3.11 Electrocardiogram Performed in Triplicate

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

Electrocardiograms should be performed in a standardized method, in triplicate, and approximately 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.

Electrocardiograms will be performed as follows:

- Three baseline ECGs will be collected ≥ 30 minutes apart, with each baseline ECG in triplicate run consecutively (ie, < 30 seconds apart; 2 sets collected at screening, and 1 set collected pre-dose on day 1 [ie, total ≥ 9 ECGs])
- Triplicate ECGs at time points after dosing

Baseline is defined as predose assessments from cycle 1 day 1. The principal investigator or designated site physician will review all ECGs. Electrocardiograms will be transferred electronically to an ECG central reader 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.

7.3.12 Clinical Laboratory Tests

The tests listed below in Table 9 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Assessments (Table 6, Table 7, and Table 8). The test results are to be recorded on the eCRFs. Missed test(s) that are not done must be reported as such on the eCRFs.

Table 9. List of Analytes

Chemistry	Hematology	Urinalysis	Coagulation	Other Labs
Sodium Potassium Bicarbonate Chloride Total protein Albumin Calcium Magnesium Phosphorus Glucose Creatinine Total bilirubin ALP AST ALT Amylase Lipase CRP LDH Uric Acid	Erythrocytes Hemoglobin Hematocrit MCV Platelets WBC Differential • Total Neutrophils • Lymphocytes • Monocytes	Specific gravity pH Blood Protein Glucose Bilirubin Ketones Microscopic exam (performed at the discretion of the investigator)	PT PTT INR Fibrinogen AT III	Pregnancy test[a] Serology (HepBsAg, HepCAb[b], anti-HBc) HIV Anti-AMG 211 antibody Tumor markers[c]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-HBc = Hepatitis B core antibody; AST = aspartate aminotransferase; AT III = Antithrombin III; CRP = C-reactive protein; HepBsAg = hepatitis B surface antigen; HepCAb = hepatitis C antibody; INR = international normalize ratio; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; sCEA = soluble carcinoembryonic antigen; WBC = white blood cell

[a] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.

[b] Polymerase chain reaction for hepatitis C RNA if HepCAb is positive.

[C] Tumor markers appropriate for the tumor indication (eg, sCEA, CA19-9) performed.

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

7.3.12.1 Serum Pregnancy Test

A serum qualitative pregnancy test will be performed locally at each site on all females unless they are surgically sterile or ≥ 2 years postmenopausal. On visits where required, the serum pregnancy test must be performed prior to dosing with investigational product. If the pregnancy test is positive at day 1 of cycle 1, the subject should not be given investigational product. If the pregnancy test is positive at any other visit, then investigational product must be held and a confirmatory quantitative serum pregnancy test must be done. If the confirmatory quantitative serum pregnancy test is positive, the investigational product (AMG 211) must be discontinued. . If the quantitative pregnancy test is negative the subject should re-start infusion per the criteria in section 6.2.1.4.3.

7.3.13 Adverse Events

Adverse event and serious adverse event assessments will be made throughout the study and will be evaluated and recorded in the source documents and on the eCRF as specified in Section 9.2.1 and Section 9.2.2, respectively. Determination of the severity of all adverse events will be consistent with the CTCAE, version 4.0 (Appendix A) unless specified otherwise.

7.3.14 Pharmacokinetic Blood Sampling

Blood samples will be obtained for determination of serum concentrations of AMG 211 at the time points specified in the Schedules of Assessments (Table 6, Table 7, and Table 8). Blood must not be drawn from the port catheter. Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

7.4 Antibody Testing Procedures

Blood samples for antibody testing are to be collected at the time points outlined in the Schedules of Assessments (Table 6, Table 7, and Table 8) for the measurement of anti-AMG 211 binding antibodies. Anti-AMG 211 antibodies in serum will be evaluated using screening and confirmatory assays. Samples that are confirmed positive for anti-drug antibodies will be tittered to determine the relative levels of anti-drug antibodies in the samples. Additional blood samples may be obtained to evaluate anti-AMG 211 antibodies' impact on AMG 211 exposure during the study.

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

7.5 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is a particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to AMG 211 and to better understand cancer.

In addition to testing the safety and effectiveness of AMG 211 in this study, the sponsor will attempt to develop tests from blood, and/or tumor biopsies (if consented) that will identify subjects that will most likely benefit from AMG 211.

Biomarker development may be pursued by use of advanced biochemical analyses, such as proteomic methods or ribonucleic acid transcript profiling.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 211.

Blood Samples

Blood samples will be collected for exploratory biomarker development at the time points listed in the Schedules of Assessments (Table 6, Table 7, and Table 8).

For all subjects, circulating free DNA (which includes tumor DNA) will be extracted from biomarker development plasma samples collected at the time points listed in the Schedules of Assessments (Table 6, Table 7, and Table 8). These samples will be used to assess potential PD response to AMG 211 by measuring changes in levels of the epigenetic CRC marker methylated Septin9.

Plasma samples may also be used to explore whether expression or mutation of specific commonly occurring mutations found in tumors tissues (and other genes based on emerging data) correlates with response to AMG 211.

Immunophenotype analysis will be used to assess whole blood by flow cytometry for biomarkers which correlate with T-cell PD responses to AMG 211 and which may be used (if consented) to identify subjects that will most likely benefit from AMG 211.

The sponsor may assess blood plasma, serum, and tumor specimens for biomarkers (eg, circulating normal/tumor cells, proteins, and transcripts) that predict response to AMG 211 and help to obtain evidence for T-cell engagement and activation associated with AMG 211 treatment.

Subjects must have archival tumor tissue available or be willing to undergo biopsy of a tumor lesion. For all subjects, tumor biopsy specimens (from archival tissue or a core biopsy) may also be used for additional testing (eg, immune histochemistry and tumor mutational analyses).

These samples will be used to help identify genes and other markers that may enhance our understanding of the cancer and/or determine how subjects respond (positively or negatively) to one or more of the investigational products being investigated.

Unless consent for optional pharmacogenetic analysis has been obtained, hereditary elements will not be analyzed.

Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

7.6 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of solid tumors and/or to identify subjects who may have positive or negative response to AMG 211. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

7.7 Sample Storage and Destruction

Any blood, blood derivative, or tumor sample collected for biomarker, anti-AMG 211 antibody, or PK analysis according to the Schedules of Assessments (Table 6, Table 7, and Table 8) can be analyzed for any of the tests outlined in the protocol and for any test necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the tumor biology and the dose response and/or prediction of response to AMG 211 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 samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.
See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol required therapies and must discuss with the subject the options for continuation of the Schedules of Assessments (Table 6, Table 7, and Table 8) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedules of Assessments and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

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

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol required therapies, protocol procedures, or the study as a whole at any time prior to study completion. Subject data and the reason(s) for termination or withdrawal from the study must be documented for the final study CSR, and it may be used for the analysis of the study.

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- Subject request
- Safety concern (eg, due to an adverse event, non-compliance, requirement for alternative therapy, protocol-required therapies, or pregnancy)
- Death
- Lost to follow-up
- Decision by sponsor (other than subject request, safety concern, or lost to follow-up)
- Confirmed disease progression as defined by modified irRC (Appendix D) or disease progression accompanied by worsening of symptoms or deterioration of the subject's general condition

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study

- Death
- Lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

Disease progression itself is not considered an adverse event; however, signs and symptoms of disease progression should be recorded as adverse events or serious adverse events. Deaths due to progressive disease during treatment until the Safety Follow-up Visit or 30 days after the protocol specified therapy, whichever is later, should be recorded as due to the primary tumor (eg, metastatic pancreatic cancer). If a new primary malignancy appears, it will be considered an adverse event.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

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

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other medically important serious event

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

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

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the EOS are reported using the applicable eCRF (eg, Adverse Event Summary).

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),

- Severity (and/or toxicity per protocol),
- Assessment of relatedness to investigational product, medical devices, or other protocol-required therapy, and
- Action taken.

If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Adverse Event Summary eCRF.

The adverse event grading scale used will be the CTCAE, version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product, medical device(s), and/or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product, medical device(s), and/or other protocol-required therapies?

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

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of investigational product or the EOS visit (whichever is later) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours of the

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

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

The investigator must assess whether the serious adverse event is possibly related to the investigational product. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product?

The investigator must assess whether the serious adverse event is possibly related to any study mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by a study activity/procedure?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs

in compliance with all reporting requirements according to local regulations and good clinical practice (GCP).

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

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur through 30 days after the last dose of protocol-required therapies.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

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

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur through 30 days after the last dose of protocol-required therapies.

Any lactation case should be reported to **Amgen Global Patient Safety** within 24 hours of the Investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoints:

- Safety: subject incidence of TEAEs, DLTs, and clinically significant changes in vital signs, ECGs, physical examination findings, and clinical laboratory tests

Secondary Endpoints:

- PK of AMG 211 after continuous intravenous (cIV) infusion across 2 cycles
- Incidence of anti-AMG 211 antibody formation
- Time to progression (TTP)

- 6-month progression-free rate
- Efficacy parameters: overall response rate (ORR; per modified irRC), duration of response, time to response

Exploratory Endpoints:

- Changes in methylation and mutations in circulating free DNA present in plasma
- Lymphocyte counts, T-cell activation and immune checkpoint regulator status
- Changes in serum cytokine levels
- Biomarkers and mutations in tumor cells
- Changes in circulating tumor cells (CTCs)
- Soluble CEA serum levels

10.1.2 Analysis Sets

The analysis of all endpoints, unless noted otherwise, will be conducted on the Safety Analysis Set defined as all subjects that are enrolled and receive at least 1 dose of AMG 211.

The analysis of DLT will be restricted to DLT-evaluable subjects. The DLT window is 28 days for all cohorts and is independent of the length of the infusion. A subject is not DLT-evaluable if he/she drops out before completion of cycle 1 for reasons other than an adverse event related to the investigational product. Ineligible subjects may be replaced.

The PK Analysis Set will contain all subjects who have received at least 1 dose of the investigational product and have at least 1 PK sample collected. These subjects will be evaluated for PK analysis unless the number of data points required for analysis is not enough, or significant protocol deviations have affected the data, or if key dosing or sampling information is missing.

10.1.3 Covariates and Subgroups

The relationship of the following covariates to efficacy endpoints will be explored if appropriate.

- Changes in methylation and mutations in circulating free DNA present in plasma
- Lymphocyte counts, T-cell activation, and immune checkpoint regulator status
- Serum cytokine levels
- Biomarkers and mutations in tumor cells
- Change in CTCs
- sCEA levels

10.2 Sample Size Considerations

It is anticipated that approximately 78 subjects will be enrolled in this study. Approximately 39 subjects will be enrolled in the dose-escalation cohorts and approximately 39 subjects will be enrolled in the dose-expansion cohorts.

The sample size in dose-escalation cohort is determined empirically and is consistent with this type of study using a modified TPI Bayesian model design (Bailey et al, 2009; Neuenschwander et al, 2008).

Refer to Appendix E for details of the modified TPI Bayesian model, the average sample size, and other design operating characteristics.

In the dose-escalation cohorts, with 3 DLT-evaluable subjects per dose level, there is a 49% to 73% probability of observing at least 1 DLT if the true DLT rate is 20% to 35%.

In the dose-expansion cohorts, with 39 subjects there is a 86% probability of observing at least one adverse event with 5% incidence rate. In the dose-expansion cohorts, an exact 80% binomial confidence interval (CI) will be provided for the ORR. With 39 subjects and 20.5% ORR, the expected 80% CI and its half-width would be 12.3% to 31.2% and 9.5%, respectively.

10.3 Planned Analyses

The following data analyses are planned: (1) dose decision analyses in the dose-escalation cohorts after every 3 to 6 DLT-evaluable subjects, (2) a safety review of dose escalation after all subjects in dose escalation have had the opportunity to complete 6 months of treatment, (3) the primary analysis after all dose-escalation and dose-expansion subjects have completed 6 months of treatment, and (4) the final analysis after all subjects have ended the study.

10.3.1 Interim Analyses

The DLRT (see Section 10.3.2) is responsible for all dose level decisions during dose escalation. Dose decisions are planned after every 3 to 6 subjects are enrolled throughout the dose-escalation cohorts. The DLRT considers the recommendation for subsequent doses based on the following rules:

- Based on the modified TPI Bayesian model, the next dose is the one with the highest probability of the target TPI (0.20, 0.35), but with a less than 0.25 probability of an excessive or unacceptable TPI.
- If ≥ 1 subject has a DLT at a dose level, then dose escalation cannot occur unless there are 6 or more DLT-evaluable subjects at that dose level. However, if a transient cytokine-release syndrome is reported as the DLT, but resolves within

48 hours and can be managed with prophylactic corticosteroids, the DLRT may decide to escalate the dose with the institution of prophylactic corticosteroid administration.

- The maximum allowed dose increase will be 1 dose level above the maximum of previous evaluated doses.
- Dose escalation can be achieved by evaluating a higher dose level with the same infusion duration (eg, 800 µg/day for 14 days to 1600 µg/day for 14 days), or by evaluating the same dose level with a prolonged infusion duration (eg, from 800 µg/day for 14 days to 800 µg/day for 28 days). The DLRT may also decide to explore in parallel both options mentioned above after the dose-escalation decision is made, or to prioritize one schedule. In this case, 2 TPI models may be run in parallel to obtain dose recommendations for these 2 schedules separately.
- Intermediate dose levels not pre-specified may be considered based on the optimal dose recommended by the TPI model.

The DLRT is responsible for making the decision to end dose escalation. Generally, the DLRT may consider the dose escalation complete if 1 of the following rules is met:

- The highest planned dose level is evaluated and no DLTs occur at any dose level. In this case the maximum administered dose will be used in a dose-expansion cohort.
- The TPI Bayesian model recommends the same dose 3 times (not necessarily sequentially).
- A total of approximately 39 DLT-evaluable subjects have been enrolled.

The Amgen Medical Monitor and Amgen Global Safety Officer can make dose decisions without convening the DRLT in the following limited circumstances:

- If a cohort has at least 3 DLT-evaluable subjects and 1 subject experiences a DLT, then the Amgen Medical Monitor and Amgen Global Safety Officer may decide to expand the number of subjects treated in this cohort.
- The Amgen Medical Monitor (or EDL) and Amgen Global Safety Officer may decide to open the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated by the DLRT.

A safety review of dose escalation is planned after all subjects in dose escalation have had the opportunity to complete 6 months of the treatment.

10.3.2 Dose Level Review Team

DLRMs will be held to review data, monitor safety, and make dose-escalation/change decisions. The review team will be composed of the investigators, Amgen Medical Monitor, Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager, Early Development Leader, and Biostatistics representative. Additional members may be added as needed (eg, PK Scientist). A quorum, defined as > 50% of the participating investigators or their qualified designee (ie, sub-investigator or

research nurse or study coordinator possessing hard copy documentation [eg, email] of the investigator's vote regarding the dose level review), must be in attendance for DLRM. The DLRM will be rescheduled if a quorum is not reached.

The following DLRT members are responsible for dosing decisions: investigators, Amgen Medical Monitor, Early Development Leader, and Amgen Global Safety Officer. Dosing decisions may include escalation to the next planned dose, escalation to an intermediate dose (a dose lower than the next planned dose), de-escalation to a lower dose; continuation, delay, or termination of dosing; or repetition or expansion of a cohort. All available study data, including demographics, investigational product administration, medical history, concomitant medications, prior surgery and therapy, adverse events, ECGs, vital signs, laboratory results, Karnofsky Performance Status, Glomerular Filtration Rate (GFR), Cancer Diagnosis and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria (including hematologic) will be reviewed and can be considered in the DLRT's decisions.

10.3.3 Safety Review

The safety review is planned after all dose-escalation subjects have had the opportunity to complete 6 months of treatment.

10.3.4 Primary Analysis

10.3.5 The Primary Analysis is Planned After all Dose-escalation and Dose-expansion Subjects Have had the Opportunity to Complete 6 Months of Treatment. Final Analysis

A final analysis is planned after all dose-escalation cohorts and dose-expansion subjects have ended the study.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Descriptive statistics will be provided for selected demographic, safety, PK, PD, and biomarker data by dose schedule and time as appropriate. Descriptive statistics on continuous data will include means, medians, SDs, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may also be presented. When data are summarized by time, the values recorded against the scheduled time points listed in the protocol will be used. When assessing minimum/maximum increases or decreases over the study, all assessments, including unscheduled assessments will be used. In general, data listings will be sorted by dose, subject, and time.

10.4.2 Primary Endpoint

A modified TPI Bayesian model will be used in the dose-escalation cohorts to estimate the MTD based on the incidence of DLTs among DLT-evaluable subjects that occur during the DLT window. Refer to Appendix E for details of the TPI Bayesian model. The MTD target TPI is (0.20, 0.35), and TPIs of (0.35, 0.60) and (0.60, 1.00) are defined as excessive and unacceptable, respectively. After each cohort, the model's recommended MTD dose for evaluation is the dose with the highest probability of the target TPI, but with a less than 0.25 probability of an excessive or unacceptable TPI. Dose-expansion will enroll additional subjects to gain further clinical experience. A final model estimate of the MTD using AMG 211 cIV dosing will be obtained utilizing all DLT-evaluable subjects from the dose-escalation cohort. Subjects who are not AMG 211 naïve at the time of enrollment will not be DLT-evaluable. Dose expansion-cohort subjects who participated in the Imaging Study are not DLT-eligible and will be excluded from this analysis. The probability of each TPI and of a DLT will be summarized by dose along with the estimated dose-toxicity curve. In addition, a sensitivity analysis will be done using data from all subjects in both dose-escalation and dose-expansion cohorts who receive at least 90% of the planned doses of investigational product during Cycle 1.

Additional summaries and/or models may be investigated, if warranted, to evaluate DLTs or other safety outcomes overall or in relation to dose, for example, all or selected related treatment-emergent adverse events leading to treatment interruption and/or discontinuation by cycle of onset.

10.4.2.1 Safety Endpoints

10.4.2.1.1 Adverse Events

Subject incidence of all treatment-emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term (PT). The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and Events of Interest (EOI) will also be provided.

10.4.2.1.2 Clinical Laboratory Tests

The analysis of safety laboratory endpoints will include summary statistics over time for each subject. Shifts in grade of safety laboratory values from baseline will also be tabulated.

10.4.2.1.3 Vital Signs

The analysis of vital signs will include summary statistics at selected time points for each subject. Shifts in vital sign values from baseline over time will be tabulated for each subject.

10.4.2.1.4 Electrocardiograms

Summaries over time and/or changes from baseline over time will be provided for all ECG parameters.

Subjects' maximum change from baseline in QT interval corrected by Fridericia's formula 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 may be plotted.

The incidence and percentage of subjects who develop anti-AMG 211 antibodies (binding) at any time will be tabulated by treatment group.

10.4.3 Secondary Endpoints

10.4.3.1 Pharmacokinetics Data Analysis

The PK parameters of AMG 211 will be determined using non-compartmental analysis methods. The following parameter will be estimated: C_{ss}, calculated as average concentration between achievement of plateau and EOI. Only in cycle 1 the following parameters will be estimated: $t_{1/2}$ and AUC_{inf}. Other parameters such as CL and V_{ss} may be estimated. Other types of analysis such as compartmental modeling may be performed if necessary dependent on the data.

Parameters will be summarized by dose level and each sampling time using means, standard deviations, medians and ranges. PK/PD modeling may be performed if data are adequate to explore the relationship between AMG 211 exposure and various PD endpoints.

10.4.3.2 Immunogenicity Analysis

Positive anti-AMG 211-antibody data will be listed and reviewed for each subject. Summaries of positive anti-AMG 211-antibody test results over time may be provided.

10.4.3.3 Efficacy Parameter Analysis

Listings will be produced for all subjects in the dose-escalation cohorts and the dose-expansion cohorts indicating the time to progression, objective response, time to response, and duration of response. The proportion of subjects with an ORR with corresponding exact 80% CI will be calculated using the Clopper-Pearson method (Clopper and Pearson, 1934) and tabulated for subjects treated at the MTD. The proportion of subjects that are progression free at 6 months with corresponding exact 80% CI will be calculated using the Clopper-Pearson method. Kaplan Meier curve will be presented for time to tumor progression with estimates for rates and 80% CI at selected weeks.

10.4.4 Exploratory Biomarkers and Pharmacodynamics

Summaries of changes from baseline over time in biomarker levels may be provided. If feasible, evidence of an association between baseline levels or presence of tumor biomarkers will be explored for objective response and PD effects.

Details of exploratory analyses may be described in a separate statistical analysis plan.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed ICF is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the demographics page, in addition to the unique subject identification number, include the age at the time of enrollment.

- For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC to Amgen.

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

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism.

However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be

provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedules of Assessments (Table 6, Table 7, and Table 8), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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

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

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2006), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events Version, version 4 (CTCAE V 4) is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

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

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF (eg, Adverse Event eCRF) 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 9.2.2.

Additional Clinical Assessments and Observation

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

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2 × ULN or INR > 1.5, retesting of liver tests, bilirubin (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:
  - Obtain complete blood count with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain 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
  - Obtain viral serologies
  - Obtain creatine phosphokinase, haptoglobin, lactate dehydrogenase, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for PK analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Electronic Serious Adverse Event Contingency Form

Completion Instructions
Electronic Serious Adverse Event (eSAE) Contingency Reporting Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, do not enter that event into the EDC system (eg, Rave) unless directed to do so by Amgen.

Header Information
Complete either Section A or Section B and follow the instructions provided within the applicable section.

Section A:
Complete this section and complete only page 1 of the SAE Report Form if the EDC system (eg, Rave) is active and your site does not have access for reasons such as: internet connectivity issues, the EDC system is down, etc.

Section B:
Complete this section and complete all pages of the SAE Report Form if:
- You are submitting a screening serious adverse event report and the database is not active yet
- You are submitting a serious adverse event report and your site access has been removed

1. **Site Information**

Site Number – Enter your assigned site number for this study

Investigator, Country, Reporter, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

Subject ID Number – Enter the entire number assigned to the subject

Date of Birth, Sex, and Race – Enter the subject's demographic information

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

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

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

Serious Adverse Event Diagnosis or Syndrome –
- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Date Started* – Enter date the adverse event first started; not when the event met serious criteria, when a diagnosis was made or when the subject was hospitalized. **This is a mandatory field.**

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

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

Serious Criteria Code* – This is a mandatory field. Enter all reasons why the reported event has met serious criteria:
- Immediately life-threatening – Use only if the subject was at **immediate** risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criteria.

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

Relationship to Amgen device – The Investigator must determine and enter the relationship of the event to the Amgen device at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field.**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

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

If you completed Section A of the form header, stop here, complete the signature section at the bottom of page 1 and fax the form to Amgen. Otherwise, complete the remainder of the form. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

Completion Instructions
Electronic Serious Adverse Event (eSAE) Contingency Reporting Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, do not enter that event into the EDC system (eg, Rave) unless directed to do so by Amgen.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

4. **Hospitalization**
   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.
5. **Investigational Product Administration**

   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label

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

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

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

   Action Taken with Product – Enter the status of the product administration.
6. **Relevant Concomitant Medications**

   Indicate if there are any relevant medications.

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

   Co-suspect – Indicate if the medication is co-suspect in the event

   Continuing – Indicate if the subject is still taking the medication

   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**

   Indicate if there are any relevant laboratory values.

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

Provide your Site Number and the Subject ID Number in the designated section at the top of Page 3.

9. **Other Relevant Tests**

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

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

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

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study 20130354 AMG 211	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

Complete either Section A *or* Section B and follow the instructions provided:

Section A

☐ **EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):**

☐ An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)

☐ Screening event (as defined by the protocol) **OR** ☐ On-study event (as defined by the protocol)

- *Complete ONLY Sections 1, 2 and 3 (page 1)*
- *Sign and date the signature section following Section 3*
- *Fax completed page of the form to the number noted in the header above Section 1*

Section B

☐ **Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):**

☐ Screening event (as defined by the protocol)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

OR

☐ Event after access to the EDC system (eg, Rave) has ended (*provide subject's End of Study date in Section 2*)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

- *Complete ALL sections of the form (all 3 pages)*
- *Sign and date the signature section at the end of the form*
- *Fax completed form (all 3 pages) to the number noted in the header above Section 1*

<<For completion by Amgen 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	Date of Birth Day Month Year	Sex ☐F ☐M	Race	If applicable, provide End of Study date

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 Serious Adverse Event Information: Day____ Month___ Year_____

Serious Adverse Event Diagnosis or Syndrome **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by IP?		**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device?			**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
					No✓	Yes✓	No✓	Yes✓	If yes, what device?		

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

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

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

AMGEN Study 20130354 AMG 211	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

If **access to the EDC system (eg, Rave) has either not begun or has ended for this study,** ***complete the remainder of this form.***

Site Number	Subject ID Number

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 administered prior to this event? ☐No ☐Yes, If yes, please complete all of Section 5

IMP: _____	Initial Start Date	Prior to, or at time of Event				Action Taken with Product
		Date of Dose	Dose	Route	Frequency	**01** Still being Administered **02** Permanently discontinued **03** Withheld
☐ (✓) Blinded	Day Month Year	Day Month Year				
☐ (✓) Open Label						

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

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

Test / Unit / Date Day Month Year												
Test												
Unit												

AMGEN Study 20130354 AMG 211	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: AMG 211 / 20130354

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ___ / dd ___ / yyyy ____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm ___ /dd ___ /yyyy ____

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

If yes, provide product (or study drug) stop date: mm ___ /dd ___ /yyyy ____

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

5. Pregnancy Information

Pregnant female's LMP mm ___ / dd ___ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ___ / dd ___ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ___ / dd ___ / yyyy ____

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

If yes, provide date of delivery: mm ___ / dd ___ / yyyy ____

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: AMG 211 / 20130354

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2. Page 1 of 1

Appendix D. Modified Immune-Related Response Criteria (irRC)

The irRC were derived from the World Health Organization (WHO) criteria to serve as guidelines to systematically characterize additional patterns of response in patients with advanced melanoma receiving ipilimumab therapy (Wolchok JD et al, 2009) and to allow the potential delayed clinical response to immune-enhancing therapies to be captured more accurately. This study will use the modified irRC as outlined below.

Antitumor response based on total measurable tumor burden

For the modified irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden).

Tumor burden assessment:

- All measurable and non-measurable lesions should be assessed at screening and at the defined tumor assessment time points.
- At baseline tumor assessment: tumor burden is the sum of the products of the 2 longest perpendicular diameters (SPD) of all index lesions (5 lesions per organ and up to 10 total lesions)
- At each subsequent tumor assessment: tumor burden is the SPD of the index lesions and of new, measurable lesions (≥ 5 × 5 mm; up to 5 new lesions per organ and 10 total lesions) are added together
  - Tumor burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

Time point response assessment using modified irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (ie, the SPD of all index lesions at screening). The modified irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the modified irRC response categories have been modified from those of WHO criteria as detailed on the overall response criteria table below.

Definitions:

Methods of measurement:

- The same imaging modality, method of assessment, and technique must be used throughout the study to characterize each identified and reported lesions.

- **MRI or CT** are the best currently available and reproducible methods to measure tumor lesions selected for response assessment. A **MRI or CT** scan should be performed with contiguous slice thickness of 5 mm or less. Subjects should be evaluated at screening for tolerance to **MRI/CT** IV contrast. Subjects intolerant of CT IV contrast (ie, allergy or renal insufficiency) should be imaged using non-contrast CT for the chest and MRI (with or without contrast) for the abdomen and pelvis to enable the best detection of disease throughout the study starting at baseline. If a subject develops a medical contradiction to the **MRI/CT** IV contrast while on study, preapproval of the sponsor is needed to switch from contrast enhanced **MRI** to non-contrast **MRI or to CT** (and vice versa).
- All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment (cycle 1 day 1).

Measurable disease: the presence of at least 1 measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

- Measurable lesions:
  - Lesions with clear borders that can be measured accurately in two dimensions (longest perpendicular diameters ≥ 10 × 10 mm with **MRI/CT** scan slice thickness no greater than 5 mm).
  - Pathologic lymph nodes is measurable when the longest diameter perpendicular to the long axis (short axis) ≥15 mm.
- Non-measurable lesions:
  - All lesions not classified as measurable lesions. At baseline assessment, non-measurable lesions including small lesions that are smaller than 10 × 10 mm with **MRI/CT** slice thickness no greater than 5 mm)
  - Truly non-measurable lesions ie, bone lesions, pleural/pericardial effusions, leptomeningeal disease, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and abdominal masses that are not confirmed and followed by imaging techniques
  - Tumor lesions situated in a previously irradiated area
  - Pathologic lymph nodes with short axis ≥ 10 mm but < 15 mm
- Index lesions:
  - All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, are to be identified as Index lesions and recorded and measured. Index lesions are to be selected on the basis of their size and their suitability for accurate repeated measurements by imaging techniques, and most representative of the subject's tumor burden.
- Non-Index lesions:
  - Measurable lesions, other than index lesions, and all sites of non-measurable disease, will be identified as non-index lesions. Non-index lesions will be evaluated at the same assessment time points as the index lesions. In subsequent assessments, changes in non-index lesions will contribute only in the assessment of complete response.

  - Pathologic lymph nodes with short axis ≥ 10 mm but < 15 mm should be considered as non-index lesions.

- Unable to evaluate (UE): Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
- Not available (NA): Scan not available
- Not Done (ND): Radiographic image of clinical measurements were not performed at this time point to evaluate the index lesions.
- Index lesion response
  - Immune-related Complete Response (irCR) – complete disappearance of all index lesions in two consecutive observations at least 4 weeks apart
  - Pathologic lymph nodes must have reduction in short axis to $\leq$ 10 mm
  - Immune-related Partial Response (irPR) – decrease of 50% or greater in tumor burden compared with baseline in two consecutive observations at least 4 weeks apart
  - Immune-related Stable Disease (irSD) - not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease
  - Immune-related Progressive Disease (irPD) – at least a 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart
    - When the size of the tumor lesion is considered 'too small to measure' (eg, less than 5 × 5 mm), a default value of 5 × 5 mm should be assigned for index lesions. If this is nadir, irPD will be judged from the tumor burden calculated using the default value.
- Non-Index Lesion Response
  - irCR – complete disappearance of all non-index lesions.
    - Pathologic lymph nodes must have reduction in short axis to < 10 mm
  - irPR – non-Index lesions are not considered in the definition of irPR
  - irSD – non-Index lesions are not considered in the definition of irSD
  - irPD – increases in number or size of non-index lesion(s) does not constitute progressive disease. New lesions that are measurable (≥ 5 × 5 mm, up to 5 new lesions per organ) are included in the calculation of tumor burden in response assessments.
- Overall response
  - irCR – complete disappearance of all lesions (whether measurable or not, and no new lesions).
    - Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date of the first documented response
  - irPR – decrease in tumor burden ≥ 50% relative to baseline.
    - Confirmation by a repeat, consecutive assessment at least 4 weeks after the first documentation

- irSD – not meeting criteria for irCR or irPR, in the absence of irPD
- irPD – increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden).).
  - Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date of the first documented assessment.

- Response confirmation:
  - irCR and irPR:
    - Must be confirmed by consecutive repeat assessments performed at least 4 weeks after the criteria for response are first met. The confirmation scan may also be performed at the next imaging assessment as defined by the schedule of assessment after the first observation.
  - irPD
    - Must be confirmed by consecutive repeat assessments performed at least 4 weeks apart in the absence of rapid clinical deterioration. The confirmation scan may also be performed at the next imaging assessment as defined by the schedule of assessment after the first observation if the subject has stable or improved clinical status. It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for subjects with a rapid decline in performance status.
    - Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should have the reason for treatment discontinuation classified as non-confirmed disease progression. In this case, irPD cannot be assigned at the time as the overall objective tumor response. Every effort should be made to document the objective progression even after discontinuation of treatment.

Measurement and Tumor Response Assessment Based on modified irRC	
Measurable lesions	• ≥ 10 × 10 mm • Pathologic lymph nodes: short axis ≥ 15 mm
Measurement of each lesion	The product of the 2 longest perpendicular diameters (cm^2)
The sum of the measurements (SPD)	• The sum of the products of the 2 longest perpendicular diameters (SPD) of all index lesions and new measurable lesions if any • Up to 5 lesions per organ and up to 10 total index lesions
Response assessment	• irPD: ≥ 25% increase from nadir (require confirmation) • irSD: < 50% decrease from baseline and < 25% increase from nadir • irPR: ≥ 50% decrease from baseline (require confirmation) • irCR: Disappearance of all lesions (require confirmation)
New Lesions	The presence of new lesion(s) does not define progression. Measurable new lesions (≥ 5 × 5 mm): The measurements of the new lesions(s) are included in the sum of the measurements.
Confirmation	Confirmation by 2 consecutive observations at least 4 weeks apart required for irCR, irPR, and irPD.

Modified irRC Overall Response Assessment			
Measurable Response	Non-measurable Response		Overall Response
Index and new, measurable lesions (tumor burden),[a] %	Non-Index lesions	New, non-measurable lesions	Using irRC
↓ 100%	Absent	Absent	irCR[b]
↓ 100%	Stable/NA	Any	irPR[b]
↓ 100%	Unequivocal progression	Any	irPR[b]
↓ ≥ 50%	Absent/Stable/NA	Any	irPR[b]
↓ ≥ 50%	Unequivocal progression	Any	irPR[b]
↓ < 50% to ↑ < 25%	Absent/Stable/NA	Any	irSD
↓ < 50% to ↑ < 25%	Unequivocal progression	Any	irSD
↑ ≥ 25%	Any	Any	irPD[b]
UE	Any	Any	UE
ND	Any	Any	UE
NA	Any	Any	UE

NA = not available; ND = not done; UE = unable to evaluate
[a] Decreased disease relative to baseline, including new measurable lesions (≥ 5× 5 mm)
[b] Response (irCR, irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart.

Appendix E. Toxicity Probability Interval (TPI) Bayesian Design

The dose-escalation cohorts will use a TPI Bayesian design to guide dose escalation. The MTD target TPI for DLT is (0.20, 0.35), and TPIs of (0.35, 0.60) and (0.60, 1.00) are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility that the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The probability of a DLT at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

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

where a and b are random variables and d_{max} is the maximum planned dose.

A minimally informative prior distribution (Neuenschwander et al, 2008) was selected for theta = (log a, log b) where the probability that the true DLT rate is ≤ 0.60 at the lowest dose (200 µg/day for 7 days) is 0.90 and the probability the true DLT rate is ≤ 0.20 at the maximum dose (6400 µg/day for 14 days) is 0.21. Median values for p_i were interpolated per the logistic model. For each d_i, 2 quantiles for p_i were selected from a Beta distribution with the target median and a precision < 2. This set of quantiles fully specified a target prior for theta. A bivariate normal distribution for theta was assumed where (log a) has a normal distribution with mean ma and standard deviation sa, and (log b) has a normal distribution with mean mb and standard deviation sb, and r is the correlation between (log a) and (log b). Numerical integration was used to calculate $\Pr[p_i \leq q(d_i)]$, where $q(d_i)$ is a quantile for dose d_i. An optimal bivariate normal distribution was estimated that achieved the minimum sum of squared difference between achieved and specified quantiles across all doses. The bivariate normal distribution prior solution has ma = 0.0536, sa = 1.685, mb = -0.1469, sb = 1.001, and r = -0.216.

The operating characteristics of the TPI Bayesian design were evaluated via simulation. The cohort size was fixed to be 3 subjects. All simulated studies started with an initial dose of 200 µg/day for 7 days and subsequent doses were selected based on the rules specified in Section 10.3.1.

The design was evaluated for two possible dose-response scenarios consistent with the design's model: "Low" and "High" MTDs. The target MTD of these 2 scenarios are set to be 1/3, and this target was set at a dose of 400 µg/day for 14 days, and 3200 µg/day for 14 days for the Low High scenarios, respectively. An "acceptable" final dose was

defined as one with the highest or second highest target TPI probability and a less than 0.25 excessive or unacceptable TPI probability. The acceptable doses by scenario were 200, 400 for Low and 1600, 3200 for High. The bivariate normal distribution for each scenario was estimated as per the prior. A Bernoulli probability for each subject in the simulations was selected from a random sample for the bivariate normal distribution for a given scenario, and a random DLT outcome for the subject was generated based on this DLT probability.

The simulation results are summarized in the table below. The average sample size increased from 15.7 to 20.8 in Low to High MTD scenarios. Early DLTs resulted in close to 5% chance of stopping with no dose selection in both cases due to the over-dose control criteria. The average Low and High final dose was about 360 and 1600 µg/d. The rate of acceptable dose selection is higher in Low scenario (83.1%), comparing with High scenario (51.4%). The average number of DLTs and DLT rate is higher in Low scenario than High scenario due to early occurrence of DLTs.

Simulation Results of TPI Model

	Low **Acceptable Dose: 200, 400**	**High** **Acceptable Dose: 1600, 3200**
Number of Subjects (IQR)	15.7 (15, 18)	20.8 (18, 24)
Acceptable Rate (95% CI)	83.1% (80.6%, 85.4%)	51.4% (48.3%, 54.5%)
No Dose Rate (95% CI)	4.5% (3.3%, 6.0%)	3.7% (2.6%, 5.1%)
Dose (IQR)	358.0 (200, 400)	1583.8 (800, 1600)
Number of DLTs (IQR)	3.8 (2, 4)	3.1 (2, 4)
DLT Rate	24.1%	15.0%

CI = confidence interval; DLT = dose-limiting toxicity; IQR = interquartile range

Appendix F. Karnofsky Performance Status and Definitions

Karnofsky Performance Status	
Score	**Description**
100%	Normal; no complaints; no evidence of disease
90%	Able to carry on normal activity; minor signs or symptoms of disease
80%	Normal activity with effort; some signs of symptoms of disease
70%	Cares for self; unable to carry on normal activity or to do active work
60%	Requires occasional assistance, but is able to care for most of his needs
50%	Requires considerable assistance and frequent medical care
40%	Disabled; requires special care and assistance
30%	Severely disabled; hospitalization is indicated although death not imminent
20%	Very sick; hospitalization necessary; active support treatment necessary
10%	Moribund; fatal processes progressing rapidly
0%	Dead

Adapted from Karnofsky et al, 1948.

Appendix G. New York Heart Association Functional Classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III	Market limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Amendment #3

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 211 Administered as Continuous Intravenous Infusion in Subjects With Relapsed/Refractory Gastrointestinal Adenocarcinoma

Amgen Protocol Number (AMG 211) 20130354

EudraCT Number 2014-000201-12

Amendment Date: 10 May 2016

Rationale:

The protocol was amended for the following reasons:

- Include the possibility of exploring alternative dose levels up to 12800 µg/d in either the 14-day or the 28-day schedule based on emerging data.
    - To date, no dose-limiting toxicity has been observed in the study and tolerability of doses up to 6400 µg/day in the 14-day schedule and 3200 µg/day in the 28-day schedule has been demonstrated (summary data presenting exposure and treatment-emergent adverse events are enclosed in document “AMG 211 20130354 Tables Exposure_Adverse Events_cutoff May16”).
- Collection of an additional on-treatment optional biopsy at cycle 2 or subsequent cycles was added to allow a better pharmacodynamic markers read-out.
- The schedule of assessments table was corrected and updated to include
    - additional Tumor Markers assessment collection at cycle 2 and all subsequent cycles, at End of Investigational Product and End of Study visits,
    - additional optional biopsy at cycle 2 or subsequent cycles,
    - specification of the ECG collection timepoints.
- Risk assessment and respective Safety language were updated to address CRS as Identified Risk and to clarify reporting of adverse events.
- Information on completed FIH study MI-CP216 was updated with final results on Clinical pharmacokinetics and clinical study data.
- Administrative, typographical and formatting changes were made throughout the protocol.

Description of Changes:

Section: Global

Change:

The version is updated to Amendment 3 and the date is updated to 10 May 2016

Section: Protocol Synopsis, Exploratory Objectives

Replace:

- Evaluate the effects of genetic variations in cancer genes and multiple other aspects of the tumor and tumor microenvironment before and following treatment with AMG 211 which may include CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes

With:

- *Evaluate the effects of genetic variations in cancer genes*
- ***Evaluate** multiple other aspects of the tumor and tumor microenvironment before and following treatment with AMG 211, which may include CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes*

Section: Protocol Synopsis, Primary Endpoint

Replace:

Safety: subject incidence of adverse events, dose-limiting toxicities (DLTs), and clinically significant changes in vital signs, electrocardiograms, physical examination findings, and clinical laboratory tests

With:

*Safety: subject incidence of **treatment emergent** adverse events **(TEAEs)**, dose-limiting toxicities (DLTs), and clinically significant changes in vital signs, electrocardiograms, physical examination findings, and clinical laboratory tests*

Section: Protocol Synopsis, Secondary Endpoints

Add acronym:

(TTP)

Section: Protocol Synopsis, Study Design

Replace:

- Dose-expansion:

  Dose-expansion will enroll additional subjects to gain further clinical experience with AMG 211.

Dose-escalation:

In dose-escalation cohorts, the planned dose levels are as follows: 200, 400, 800, 1600, 3200, and 6400 µg/day. Alternative dose levels up to 12800 µg/d will be explored based on emerging data.

With:

- *Dose-expansion*:

  ***The** dose-expansion will enroll additional subjects to gain further clinical experience with AMG 211.*

Dose-escalation:

*In dose-escalation cohorts, the planned dose levels are as follows: 200, 400, 800, 1600, 3200, and 6400 µg/day. Alternative dose levels **up to 12800 µg/d will** be explored in **either the 14-day or 28-day schedule** based on emerging data.*

Section: Protocol Synopsis, Summary of Subject Eligibility Criteria

Typo correction

Replace:
Subjects must have at least 1 measureable tumor lesion per the modified irRC (Appendix D) and adequate hematological, renal, and liver function.

With:
Subjects must have at least 1 **measurable** tumor lesion per the modified irRC (Appendix D) and adequate hematological, renal, and liver function.

Section: Protocol Synopsis, Statistical Considerations

Replace:
The Amgen Medical Monitor and Amgen Global Safety Officer can make dose decisions without convening the DLRT in the following limited circumstances:

- If a cohort has at least 3 DLT-evaluable subjects and 1 subject experiences a DLT, then the Amgen Medical Monitor and Amgen Global Safety Officer may decide to expand the number of subjects treated in this cohort.
- The Amgen Medical Monitor and Amgen Global Safety Officer may decide to open the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated by the DLRT.

With:

*The Amgen Medical Monitor **(or EDL)** and Amgen Global Safety Officer can make dose decisions without convening the DLRT in the following limited circumstances:*

- *If a cohort has at least 3 DLT-evaluable subjects and 1 subject experiences a DLT, then the Amgen Medical Monitor and Amgen Global Safety Officer may decide to expand the number of subjects treated in this cohort.*
- *The Amgen Medical Monitor **(or EDL)** and Amgen Global Safety Officer may decide to open the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated by the DLRT.*

Section: Study Design and Treatment Schema

Add:

**** Depending on the safety data from the 6400 µg/day cohorts, a level of 12800 µg/day can be added, if agreed by the DLRT. The longest schedule allowing highest dose intensity (14-day or 28-day infusion) found to be tolerated will be selected for the additional cohort.***

Section: Study Glossary

Add:

CRS	***Cytokine Release Syndrome***
EDL	**Early Development Lead**
TEAEs	**Treatment Emergent Adverse Events**
TTP	**Time to progression**

Replace:

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

With:

EOIP	*End of **Investigational Product**. Defined as the last assessment for the protocol specified treatment phase of the study for an individual subject*

Section: 1.2 Secondary

Replace:

Evaluate time to progression and to evaluate the proportion of subjects progression-free at 6 months

With:

*Evaluate time to progression **(TTP)** and evaluate the proportion of subjects progression-free at 6 months*

Section: 1.3 Exploratory

Replace:

- Evaluate the effects of genetic variations in cancer genes and multiple other aspects of the tumor and tumor microenvironment before and following treatment with AMG 211 which may include carcinoembryonic antigen (CEA) expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes

With:

- *Evaluate the effects of genetic variations in cancer genes*
- ***Evaluate** multiple other aspects of the tumor and tumor microenvironment before and following treatment with AMG 211 which may include carcinoembryonic antigen (CEA) expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes*

Section: 2.2.1 Nonclinical Pharmacology

Replace:

Detailed information about the nonclinical pharmacology can be found in the MEDI-565 (AMG 211) Investigator Brochure (MedImmune, 2014).

With:

*Detailed information about the nonclinical pharmacology can be found in the **current version of the** MEDI-565/AMG 211 Investigator Brochure.*

Section: 2.2.3 Clinical Pharmacokinetics

Replace:

The PK of AMG 211 (MEDI-565) was evaluated in Study MI-CP216. AMG 211 was administered by intravenous (IV) infusion over 3 hours per day for 5 consecutive days (ie, days 1 through 5) every 28 days (defined as 1 cycle). Interim PK data analyses were conducted for the first 11 cohorts, through the 3 mg dose without dexamethasone and the 1.5-mg dose with dexamethasone. Serum AMG 211 concentrations versus time profiles are shown in Figure 1. Pharmacokinetic parameters estimated by non-compartmental methods are shown in Table 1. Following IV infusion, the peak serum concentrations of AMG 211 increased approximately dose-proportionally from 0.48 µg/mL at the 0.75 µg dose level to 321 ng/mL at the 3 mg dose level. AMG 211 concentrations decreased rapidly after the end of infusion (EOI) with a short terminal elimination phase half-life of 2 to 5 hours. Clearance (CL) ranged from 45 to 73 L/day

(average value = 55 L/day = 2.3 L/hr) and the volume of distribution at steady state (Vss) ranged from 6 to 11 L (average value = 8.0 L) across the dose groups. At the highest dose tested to date (3 mg), mean maximum plasma concentration (Cmax) at the EOI was 321 ng/mL, which decreased to 2.7 µg/mL within 24 hours. There was no notable accumulation between doses within a cycle and the PK was similar across cycles for a given dose. Trough concentrations at 24 hours post dose were below the limit of quantification (BLQ) in subjects receiving doses of 0.75, 2.25, 6.75, 20, and 60 µg (see Table 1). The area under the concentration-time curve from time zero to infinity (AUCinf) increased in a dose proportional manner over the range of 60 to 3000 µg. AMG 211 PK was comparable at the 1.5 mg dose level with (Cohort 11) or without (Cohort 9) dexamethasone co-administration, indicating dexamethasone had no effect on AMG 211 PK (see Table 1).

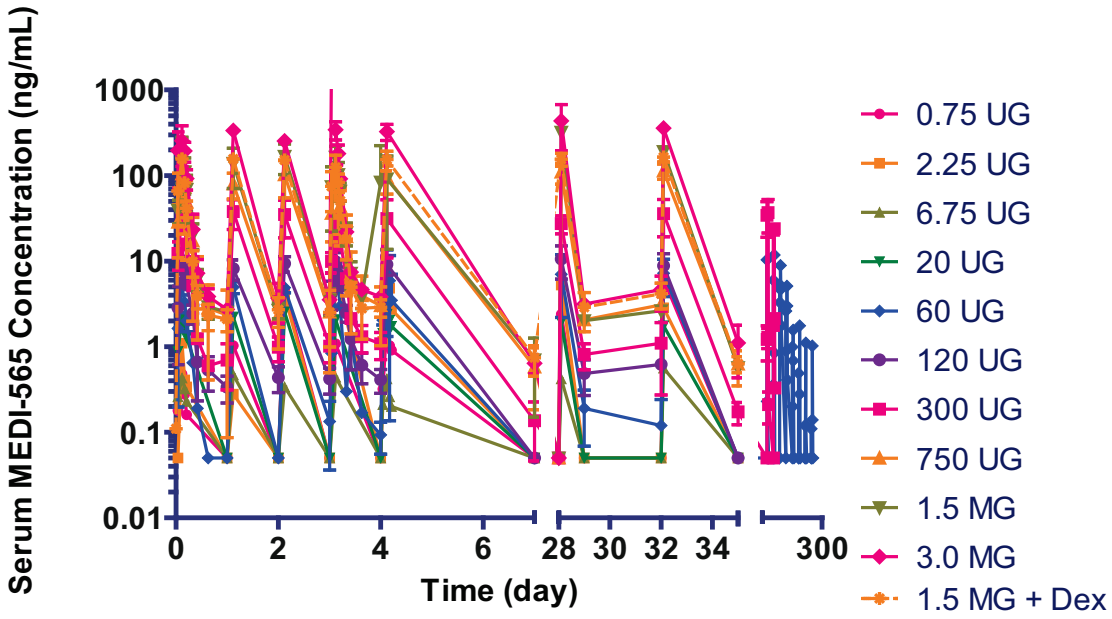
With:

The PK of AMG 211 (MEDI-565) was evaluated in Study MI-CP216. AMG 211 was administered by intravenous (IV) infusion over 3 hours per day for 5 consecutive days (ie, days 1 through 5) every 28 days (defined as 1 cycle). PK data analyses were conducted for ***all*** *cohorts.* ***PK for cohorts at 1.5 mg and 3.0 mg doses were analyzed with and*** *without dexamethasone. Serum AMG 211 concentrations versus time profiles are shown in Figure 1. Pharmacokinetic parameters estimated by non-compartmental methods are shown in Table 1. Following IV infusion, the peak serum concentrations of AMG 211 increased approximately dose-proportionally from 0.****5*** *µg/mL at the 0.75 µg dose level to* ***652.7*** *ng/mL at the* ***7.5*** *mg dose level. AMG 211 concentrations decreased rapidly after the end of infusion (EOI) with a short terminal elimination phase half-life of 2****.2*** *to* ***6.****5 hours. Clearance* ***after the first dose*** *ranged from* ***35 to 77*** *L/day, volume of distribution ranged from* ***5*** *to* ***12 L, and half-life ranged from 2 to 6.5 hours.*** *At the highest dose tested (****7.5*** *mg), mean maximum plasma concentration (Cmax) at the EOI was* ***652.7*** *ng/mL, which decreased to* ***14.5*** *µg/mL within 24 hours. There was no notable accumulation between doses within a cycle and the PK was similar across cycles for a given dose. Trough concentrations at 24 hours post dose were below the limit of quantification (BLQ) in subjects receiving doses of 0.75, 2.25, 6.75, 20, and 60 µg (see Table 1). AMG 211 PK was comparable at 1.5 mg* ***and 3 mg*** *dose level with or without dexamethasone co-administration, indicating dexamethasone had no effect on AMG 211 PK (see Table 1).*

Section: 2.2.3 Clinical Pharmacokinetics, Figure 1

Replace:

Serum MEDI-565 (AMG 211) Concentration Versus Time Profiles Following IV Infusion (N = 1 to 5 per Dose Cohort)



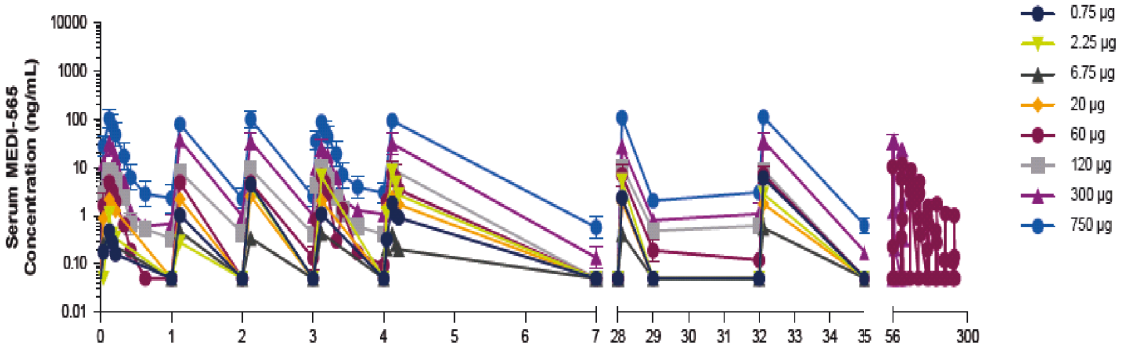
With:

Mean MEDI-565/AMG 211 Serum Concentrations Following Repeated Intravenous Infusions in Patients With Gastrointestinal Adenocarcinomas

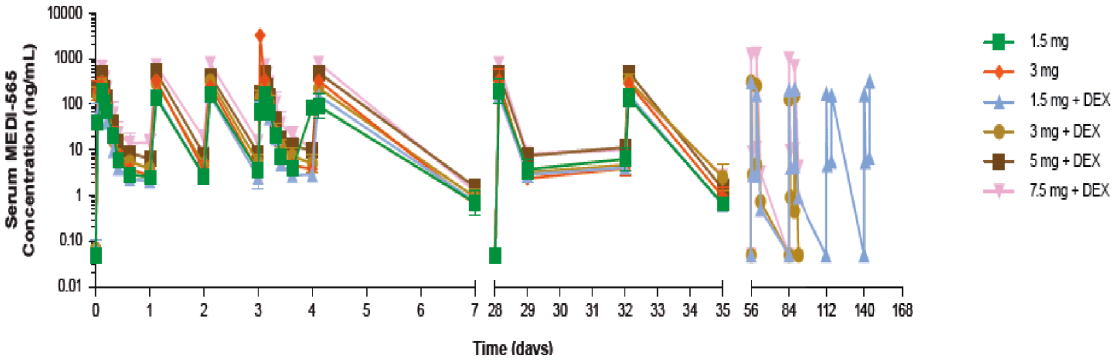
Pharmacokinetic profile of (A) low-dose cohorts (MEDI-565 0.75 µg–750 µg) and (B) high-dose cohorts (MEDI-565 1.5 mg–7.5 mg).

Abbreviation: DEX = dexamethasone.

A.



B.



Section: 2.2.3 Clinical Pharmacokinetics, Table 1

Replace:

Table 1. Pharmacokinetic Parameters for MEDI-565 (AMG 211)

Dose, µg	N	C_{max}, ng/mL Mean (SD)	$C_{24\ hr}$, ng/mL Mean (SD)	AUC_{inf}, ng/mL*day Mean (SD)	Clearance, L/day Mean (SD)	V_{ss}, L Mean (SD)	Half-life, hours Mean (SD)
0.75	1	0.48 (NA)	BLQ (NA)	NA	NA	NA	NA
2.25	1	1.1 (NA)	BLQ (NA)	NA	NA	NA	NA
6.75	1	0.43 (NA)	BLQ (NA)	NA	NA	NA	NA
20	1	2.23 (NA)	BLQ (NA)	NA	NA	NA	NA
60	3	4.95 (0.92)	BLQ (NA)	0.82 (0.034)	73.2 (3.11)	8.32 (3.23)	1.71 (0.694)
120	3	9.06 (2.6)	0.34 (0.12)	2.26 (0.341)	54 (8.94)	10.7 (3.13)	3.17 (1.23)
300	3	31.8 (6.8)	0.7 (0.38)	6.67 (0.283)	45 (1.87)	7.33 (1.66)	2.78 (0.698)
750	3	104 (58.4)	2.34 (2.25)	21 (12.3)	46.5 (29.3)	5.92 (1.82)	2.93 (0.192)
1500	3	180 (98.9)	2.53 (0.28)	30.2 (11.8)	54.8 (20.3)	7.81 (3.08)	2.47 (0.73)
3000	5	321 (102)	2.74 (0.08)	50 (8.34)	61.5 (11.1)	6.08 (2.39)	2.52 (1.29)
1500 + Dex	3	156 (11.8)	2.1 (0.6)	30.6 (8.9)	52 (1.5)	10 (4)	4.9 (0.9)

With:

Table 1. Pharmacokinetic Parameters of MEDI-565/AMG 211 After First Dose

MEDI-565 Dose	n	C_{max} (ng/mL) (SD)	C_{24h} (ng/mL) (SD)	AUC_{last} (ng•day/ mL) (SD)	AUC_{inf} (ng•day/ mL) (SD)	CL (L/day) (SD)	$t_{1/2}$ (hr) (SD)	V_{ss} (L) (SD)
0.75 µg	1	0.5 (NC)	NC	0.05 (NC)	NC	NC	NC	NC
2.25 µg	1	1.1 (NC)	NC	0.1 (NC)	NC	NC	NC	NC
6.75 µg	1	0.4 (NC)	NC	0.06 (NC)	NC	NC	NC	NC
20 µg	1	2.2 (NC)	NC	0.3 (NC)	NC	NC	NC	NC
60 µg	3	5.0 (0.9)	NC	0.7 (0.1)	0.8 (NC)	77.0 (NC)	2.2 (NC)	10.8 (NC)
120 µg	3	9.1 (2.6)	0.3 (0.1)	2.3 (0.3)	2.5 (0.02)	48.0 (0.4)	4.4 (1.2)	10.2 (3.5)
300 µg	3	31.8 (6.8)	0.7 (0.4)	9.0 (2.3)	9.1 (2.3)	34.5 (9.6)	3.5 (0.4)	5.2 (1.6)
750 µg	3	104.4 (58.4)	2.3 (2.3)	20.7 (11.9)	21.3 (12.4)	45.8 (28.9)	4.0 (0.6)	6.5 (2.3)
1.5 mg	3	180 (98.9)	2.6 (0.3)	30.1 (11.6)	30.6 (11.6)	53.9 (19.6)	3.5 (0.4)	8.6 (3.6)
3 mg	5	321.3 (102.0)	2.7 (0.1)	50.5 (9.3)	51.2 (9.3)	60.3 (11.8)	3.5 (1.5)	6.6 (2.0)
1.5 mg/ DEX	3	156.3 (11.8)	2.1 (0.6)	29.7 (9.7)	30.2 (9.8)	53.2 (16.7)	4.4 (1.2)	7.1 (2.6)
3 mg/ DEX	3	297.0 (68.8)	4.0 (1.1)	49.2 (6.1)	50.7 (7.0)	59.9 (7.7)	6.5 (2.5)	8.6 (0.3)
5 mg /DEX	6	506.2 (70.3)	6.4 (1.5)	80.3 (14.1)	82.1 (14.2)	62.3 (9.8)	5.0 (1.4)	8.9 (2.3)
7.5 mg/ DEX	3	652.7 (31.3)	14.5 (7.7)	108.3 (18.4)	111.2 (28.6)	69.8 (17.9)	5.3 (0.8)	12.0 (0.6)

Abbreviations: NC = not calculated

Replace:

The average CL of 2.3 L/hr (ie, 55 L/day) and the average Vss of 8.0 L from study MI-CP216 were used for simulation using a one-compartment PK model. The predicted AUCinf and steady-state drug concentration in plasma during constant-rate infusion (Css) at any given cIV infusion dose of AMG 211 can be calculated using the following equations: daily AUCinf = daily dose/CL; Css = Ro/CL, where Ro is the dosing rate in µg/day. Predicted PK profiles and exposure after cIV dose rate of 200 to 6400 µg/day are shown below (Figure 2 and Table 2).

With:

*The average CL of 2.3 L/hr (ie, 55**.2** L/day) and the average V_{ss} of 8.0 L **observed in cohorts 1 to 11** from study MI-CP216 were used for simulation using a one-compartment PK model. The predicted AUCinf and steady-state drug concentration in plasma during constant-rate infusion (Css) at any given cIV infusion dose of AMG 211 can be calculated using the following equations: daily AUCinf = daily dose/CL; Css = Ro/CL, where Ro is the dosing rate in µg/day. Predicted PK profiles and exposure after cIV dose rate of 200 to **12800** µg/day are shown below (Figure 2 and Table 2).*

Section: 2.2.3 Clinical Pharmacokinetics, Table 2

Replace:

Predicted Mean Exposure to AMG 211 After cIV Infusion Dosing of 200 to 6400 µg/day for 14 Days Using Average Clearance of 2.3 L/hr

	Dose (µg/day)					
Parameter	200	400	800	1600	3200	6400
C_{ss} (ng/mL)	3.6	7.2	14.5	29.0	58.0	116
Total AUC per 14-day cycle (hr*ng/mL)[a]	1217	2435	4870	9739	19478	38957
Daily AUC (hr*ng/mL)[b]	87	174	348	696	1391	2783

With:

*Predicted Mean Exposure to AMG 211 After cIV Infusion Dosing of 200 to **12800** µg/day for 14 Days Using Average Clearance of 2.3 L/hr*

	Dose (µg/day)						
Parameter	*200*	*400*	*800*	*1600*	*3200*	*6400*	***12800***
C_{ss} (ng/mL)	*3,6*	*7,2*	*14,5*	*29*	*58*	*116*	***232***
*Total AUC per 14-day cycle (hr*ng/mL)[a]*	*1217*	*2435*	*4870*	*9739*	*19478*	*38957*	***77915***
*Daily AUC (hr*ng/mL)[b]*	*87*	*174*	*348*	*696*	*1391*	*2783*	***5565***

Section: 2.2.4 Clinical Data from First-in-Human Study with MEDI-565/AMG 211

Replace tittle section:

2.2.4 Clinical Data from First-in-Human Study with AMG 211

With:

*2.2.4 Clinical Data from First-in-Human Study with **MEDI-565**/AMG 211*

Replace:

A phase 1 FIH study (MI-CP216) is being conducted by MedImmune with MEDI-565 (AMG 211) using a daily 3-hour IV infusion for 5 consecutive days in a 28-day cycle. Dose escalation proceeded from daily dose levels of 0.75 µg up to 3 mg/day. At the 3 mg/day dose level 2 dose-limiting toxicities (DLTs; grade 3 hypoxia within 12 hours of infusion start on day 1 in both subjects) were observed. The study was amended to include administration of dexamethasone before AMG 211 is administered (steroid prophylaxis) for presumed inflammatory/cytokine mediated toxicities. Dosing resumed in the amended study at 1.5 mg/day which was deemed tolerable. A cohort of 3 subjects has been exposed at 3 mg/day with steroid prophylaxis. These subjects all tolerated the infusion period without a DLT. Further dose escalation is ongoing. By March 2014, a total of 33 subjects have been exposed without the observation of further DLT.

With:

*A phase 1 FIH study (MI-CP216) **was** conducted by MedImmune with MEDI-565 (AMG 211) **in the United States. This was a Phase 1, multicentre, open-label, single-arm dose-escalation and optional dose-expansion study to evaluate the safety, tolerability, PK, immunogenicity, and anti-tumor activity. In Study MI-CP216, AMG 211 was given by IV infusion over 3 hours per day for 5 consecutive days of a 28-day cycle (ie, short-term infusion) in adult subjects who had refractory gastrointestinal adenocarcinomas for which no standard or curative therapies are available. The study consisted of an initial dose-escalation phase to determine the maximum tolerated dose (MTD) or optimum biologic dose (OBD). The dose escalation phase was followed by an optional dose expansion phase at the MTD/OBD. However, in January 2015, the sponsor (MedImmune) made a decision not to start the dose-expansion phase of the study due to a lack of efficacy, as no objective response per the Response Evaluation Criteria in Solid tumors was observed. The decision to stop the study was not related to any safety issues.***

Dose escalation proceeded from daily dose levels of 0.75 µg up to 3 mg/day. At the 3 mg/day dose level 2 dose-limiting toxicities (DLTs; grade 3 hypoxia within 12 hours of infusion start on day 1 in both subjects) were observed.

The study was amended to include administration of dexamethasone before ***MEDI-565/****AMG 211 is administered (steroid prophylaxis) for presumed inflammatory/cytokine mediated toxicities. Dosing resumed in the amended study at 1.5 mg/day which was deemed tolerable. A cohort of 3 subjects has been exposed at 3 mg/day with steroid prophylaxis. These subjects all tolerated the infusion period without a DLT.*

In total, four patients (2 at 3 mg and 2 at 7.5 mg + dexamethasone) experienced DLTs: hypoxia (n=2), diarrhea (n=1), and cytokine release syndrome (CRS; n=1). The MTD was determined to be MEDI-565 5 mg with dexamethasone premedication. The most common treatment-emergent adverse events were nausea, abdominal pain, vomiting, and fatigue (Table 2). Grade 3 treatment-related adverse events were observed in 5 patients and included diarrhea, CRS, increased alanine aminotransferase, hypertension (all, n=1), and hypoxia (n=2). Six serious treatment-related adverse events were reported in 5 patients and included diarrhea, vomiting, pyrexia, CRS (all, 1 event), and hypoxia (2 events).
Five patients were discontinued from treatment because of adverse events, including diarrhea, CRS, and central nervous system metastases (all, n=1), and hypoxia (n=2).

Nineteen patients (48.7%) had ADAs; 5 (12.8%) had high titers, 2 with decreased MEDI-565/AMG 211 concentrations. No objective responses occurred; 11 (28%) had stable disease as best response

Study 20130354 (phase 1) is the ongoing Phase 1 study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of AMG 211 administered as continuous intravenous infusion (cIV) in subjects with relapsed/ refractory gastrointestinal adenocarcinoma. As of April 2016, approximately 32 subjects received AMG 211 for up to 6400 µg/cIV without any DLT.

Section: 2.3 Risk Assessment

Replace:

At this time, there is limited clinical experience with AMG 211 in humans. No identified risks have been defined to date. Refer to the MEDI-565 (AMG 211) Investigator's Brochure, Section 5.5 for the list of the potential risks (MedImmune 2014).

With:

At this time, there is limited clinical experience with AMG 211 in humans ***from one completed FIH study sponsored by MedImmune (study MI-CP216) and approximately 32 subjects enrolled in this ongoing study 20130354. Cytokine Release Syndrome (CRS) has*** *been defined* ***as an Important Identified Risks*** *to date. Refer to the AMG 211/MEDI-565 Investigator's Brochure* ***(appendix A, Developmental Core Safety Information and to*** *Section* ***5.4****) for the list of the potential risks.*

Section: 2.4 Rationale

Replace:

The first phase 1 study of AMG 211 (MI-CP216) has investigated a 3-hour infusion for 5 consecutive days of a 28-day cycle. While subjects have been dosed at levels as high as 3 mg/day, no objective responses have been observed.

With:

The first phase 1 study of ***MEDI-565/****AMG 211 (MI-CP216) investigated a 3-hour infusion for 5 consecutive days of a 28-day cycle. While subjects* ***were*** *dosed at levels as high as* ***7.5*** *mg/day, no objective responses* ***were*** *observed.*

Replace:

No objective responses have been observed to date although AMG 211 C_{max} serum levels of up to 321 ng/mL and trough levels of up to 2.7 ng/mL were achieved. In addition, approximately 80% of subjects (19/24 subjects) discontinued treatment after a maximum of 2 cycles because of disease progression

With:

No objective responses ***were*** *observed although AMG 211* C_{max} *serum levels of up to* ***652.7*** *ng/mL and trough levels of up to* ***14.5*** *ng/mL were achieved. In addition, approximately 80% of subjects (19/24 subjects)* ***treated with up to a dose of 3 mg/day*** *discontinued treatment after a maximum of 2 cycles because of disease progression.*

Section: 3.1 Study Design

Replace:

Dose-expansion will enroll additional subjects to gain further clinical experience with AMG 211.

With:

The *dose-expansion will enroll additional subjects to gain further clinical experience with AMG 211.*

Replace:

Alternative dose levels may be explored based on emerging data.

With:

Alternative dose levels ***up to 12800 µg/day*** *will be explored* ***in either the 14-day or 28-day schedule*** *based on emerging data.*

Section: 3.1 Study Design, Table 3 Study Design Overview

Replace:

Part	Cohort [b]	Dose Level	Number of Subjects
Dose Escalation	1	200 µg/d for 7 days in cycle 1 200 µg/d for 14 days in cycle 2 and all subsequent cycles	3-6
	2	200 µg/d for 14 days in all cycles	3-6
	3	400 µg/d for 14 days in all cycles	3-6
	4	800 µg/d for 14 days in all cycles	3-6
	5	1600 µg/d for 14 days in all cycles	3-6
	6	3200 µg/d for 14 days in all cycles	3-6
	7	6400 µg/d for 14 days in all cycles	3-6
28-day Schedule	X-1[a]	Dose Level -1 of 14-day Schedule × 28 days	3-6
	X-2[a]	MTD × 28 days	3-6
Dose Expansion	A	MTD or lower dose	39

With:

Part	Cohort	Dose Level	Number of Subjects
Dose Escalation [b]	1	200 µg/d for 7 days in cycle 1 200 µg/d for 14 days in cycle 2 and all subsequent cycles	3-6
	2	200 µg/d for 14 days in all cycles	3-6
	3	400 µg/d for 14 days in all cycles	3-6
	4	800 µg/d for 14 days in all cycles	3-6
	5	1600 µg/d for 14 days in all cycles	3-6
	6	3200 µg/d for 14 days in all cycles	3-6
	7	6400 µg/d for 14 days in all cycles	3-6
	8*	**12800 µg/d for 14 or 28 days in all cycles**	**3-6**
28-day Schedule	X-1[a]	Dose Level -1 of 14-day Schedule × 28 days	3-6
	X-2[a]	MTD × 28 days	3-6
Dose Expansion	A	MTD or lower dose **or highest dose tested without reaching MTD**	39

Add:

**** Alternative dose level up to 12800 µg/day will be explored in either the 14-day or 28-day schedule based on emerging data.***

Section: 6.2.1.1 Dosage, Administration, and Schedule

Replace:

Alternative dose levels may be explored based on emerging data.

With:

*Alternative dose levels **up to 12800 µg/day** will be explored **in either the 14-day or the 28-day schedule** based on emerging data.*

Replace:

Administration of the premedication (eg, dexamethasone) for cytokine-release associated symptoms is allowed at higher dose levels after consultation with the sponsor (see Section 6.5).

With:

*Administration of the premedication (eg, dexamethasone) **to minimize the risk of** cytokine-release **syndrome** symptoms **is recommended for all treatments** at **a** dose **of 800 µg/day or higher** (see Section 6.5).*

Replace:

Longer breaks of up to 8 weeks between treatment cycles will be allowed for subjects who remain on study treatment beyond 24 weeks from start of study treatment.

With:

Longer breaks of up to 8 weeks between treatment cycles will be allowed for subjects who remain on study treatment beyond 24 weeks from start of study treatment ***or in the event of urgent reasons other than adverse events related to study drug.***

Section: 6.2.1.2 AMG 211 Outpatient Dosing

Add:

Prophylactic treatment with steroid (eg, dexamethasone) is recommended before restarting of AMG 211 if clinically indicated.

Section: 6.2.1.3 Dose-cohort Study Escalation and Stopping Rules Dose-limiting Toxicities (DLT)

Replace:

The **CTCAE** will be used to assess toxicities/adverse events.

With:

The ***Common Terminology Criteria for Adverse Events*** *(CTCAE* ***version 4.03****) will be used to assess toxicities/adverse events.*

Add:

Cytokine release syndrome manageable with symptomatic treatment and/or infusion interruption of up to 2 days

Replace:

For certain toxicities such as laboratory assessments without a clear clinical correlation (eg, lipase increase without signs of a clinical pancreatitis), a discussion between the investigator and the sponsor may take place if that adverse event should be assessed as a DLT.

With:

For certain toxicities such as laboratory ***abnormalities*** *without a clear clinical correlation (eg, increase* ***in serum*** *lipase* ***level*** *without signs* ***or symptoms*** *of a clinical pancreatitis), a discussion between the investigator and the sponsor may take place* ***whether*** *that adverse event should be assessed as a DLT.*

Section: 6.2.1.4.1 Dose Reduction, Table 5

Replace:

CTCAE Grade	Dose Delay	Dose Reduction	Comment
Non-hematological			
Infection, cytokine release syndrome, tumor lysis syndrome, diarrhea, hypoxia			
3	Delay until ≤ grade 1	Restart at 1 dose level lower	Consider re-escalation if completely recovered and no new toxicity occurred within 7 days of infusion Permanent discontinuation of study treatment if no recovery within 21 days
All other non-hematological toxicities and clinically significant laboratory parameters			
3	Delay until ≤ grade 2	Resolution to grade 1 or 2: Restart at 1 dose level lower Resolution to normal within 1 week or a relationship to study drug can be ruled out: No change	Investigator may decide to continue infusion for up to 72 hours if toxicity has not occurred during the DLT window and is responding to treatment or represents an asymptomatic laboratory change Permanent discontinuation of study treatment if no recovery within 21 days

With:

CTCAE Grade	Dose Delay	Dose Reduction	Comment
Non-hematological			
Infection, cytokine release syndrome, tumor lysis syndrome, diarrhea, hypoxia			
3	Delay until ≤ grade 1	Restart at 1 dose level lower	Consider re-escalation if completely recovered and no new toxicity occurred within 7 days of infusion. Permanent discontinuation of study treatment if no recovery within 21 days. **Start at the same dose if resolved cytokine release syndrome, infection, tumor lysis syndrome, or hypoxia.**
All other non-hematological toxicities and clinically significant laboratory parameters			
3	Delay until ≤ grade 2	Resolution to grade 1 or 2: Restart at 1 dose level lower Resolution to normal within 1 week or a relationship to study drug can be ruled out: No change	**Per the** Investigator **medical discretion to** decide **whether** to continue **the** infusion for up to 72 hours if toxicity has not occurred during the DLT window and **if the toxicity or abnormal labs are** responding to treatment or represents an asymptomatic laboratory change. Permanent discontinuation of study treatment if no recovery within 21 days

Section: 6.2.1.4.2 Infusion Interruption

Replace:

Significant events requiring a change in treatment will be managed by immediate infusion interruption and this, including treatment interruption, must be documented in the eCRF:

With:

*Significant events requiring a change in treatment will be managed by **an** immediate infusion interruption **of equal or less than 24 hours. Both, infusion interruptions** and treatment interruptions **greater than 24 hours, have to** be documented in the eCRF:*

Section: 6.2.1.4.3 Restarting the Infusion

Delete:

If the subject has received prophylactic treatment with corticosteroids at infusion start, corticosteroids also need to be administered prior to the restart if the treatment was interrupted for a period > 48 hours

Add:

Prophylactic treatment with steroid (eg, dexamethasone) is recommended before restarting of AMG 211 if clinically indicated.

Section: 6.2.1.4.4 Permanent Discontinuation

Replace:

In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the End of Treatment (EOT) and EOS visits.

With:

*In any case of premature treatment discontinuation, the investigator should make every effort to perform all examinations scheduled for the **EOIP** and EOS visits.*

Delete:

Subjects with progressive disease fulfill a study endpoint and are discontinued as per protocol.

Section: 6.4.1 Criteria for Permanent Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

Add:

*Nonalcoholic Fatty Liver Disease including steatohepatitis **(NASH)***

Add:

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or severity of the hepatotoxicity or event) if Amgen IP and other protocol-required therapies should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

Section: 6.5 Concomitant Therapy

Replace:

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

With:

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

Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.7.

Replace:

Subjects experiencing persistent (> 24 hours) or severe cytokine-release associated symptoms may be treated with IV paracetamol or metamizole, steroids, and anti-histamines, at the investigator's discretion. In this case an unscheduled blood sample should be collected to measure cytokine levels. For symptomatic treatment of fever > 38.5°C metamizole as infusion and/or paracetamol, ibuprofen, or acetylsalicylic acid are recommended.

If any subject experiences an initial toxicity responsive to dexamethasone treatment, the sponsor may recommend treating all subsequent subjects with prophylactic dexamethasone according to the following:

- Dexamethasone at a dose of 8 mg or equivalent corticosteroid will be administered
  - 8 to 12 hours prior to the start of the infusion on day -1
  - 1 hour prior to the start of the infusion on day 1
  - Every 8 to 12 hours after start of infusion on days 1 and 2
- Corticosteroid treatment can be continued if deemed necessary by the investigator, and after consultation with the sponsor but doses should be tapered as quickly as feasible

Further variations may be needed that should be discussed and agreed upon in a Dose Level Review Meeting (DLRM).

With:

For symptomatic treatment of fever > 38.5°C metamizole as infusion and/or paracetamol, ibuprofen, or acetylsalicylic acid are recommended.

Patients should be closely monitored for any signs and symptoms that may be associated with CRS such as pyrexia, headache, nausea, vomiting, asthenia,

hypotension, hypoxia and tachycardia during the initiation of AMG 211 treatment. To mitigate the CRS risk prophylactic treatment with steroids (dexamethasone) is recommended to be administered before the first dose (initial cycle) of AMG 211, and before subsequent cycles of AMG 211 (if clinically indicated). In the event of CRS, an unscheduled blood sample should be collected to measure cytokine levels.

The *sponsor may recommend treating subjects with prophylactic dexamethasone according to the following:*

- *Dexamethasone at a dose of 8 mg or equivalent corticosteroid will be administered*
  - *8 to 12 hours prior to the start of the infusion on day -1*
  - *1 hour prior to the start of the infusion on day 1*
  - *Every 8 to 12 hours after start of infusion on days 1 and 2*
- *Corticosteroid treatment can be continued if deemed necessary by the investigator and after consultation with the sponsor but doses should be tapered as quickly as feasible.*

Further variations may be needed that should be discussed and agreed upon in a Dose Level Review Meeting (DLRM).

Section: 6.7 Excluded Treatments and/or Procedures During Study Period

Add:

- *Participation in an investigational study (drug or device) within 28 days of study day 1.* ***Exception to this criterion is the participation in the optional Imaging Study and all procedures related to this study****.*

Section: 7.1, Table 6 Footnote

Replace:

EOT = End of Treatment

With:

*EO****IP*** *= End of* ***Investigational Product***

Section: 7.1, Table 7

Replace:

	SCR	Treatment Period																															
Cycle		1																					2 and all subsequent cycles[k]								Q2C	EOT	EOS
Study Day	-14 to -1[i]	1										2	3-5	8	11	15					16	22	1			2	3-5	8	15	22			
Hours		Pre-dose	Relative to start of infusion													Relative to EOI							Pre-dose	Relative to start of infusion									
			0-1.5	2	3	4	6	8	12	14	20	24	48-96	168		EOI	0.5	2	4	8	24			0	6	24	48-96	168	336				
GENERAL ASSESSMENTS																																	
Informed consent	X																																
Hospitalization							X[c]																		X[c]								
Concomitant medications	X	X →	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X
Adverse events	X	X →	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		X	X
Clinical evaluation[a]	X	X										X	X	X	X	X					X	X	X			X	X	X	X	X		X	X
Vital signs, pulse oximetry	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		X[i]	X	X	X	X	X		X	X
12-lead ECG (triplicate measurement)	X	X										X				X						X	X[e]			X[e]				X[e]			X
LABORATORY ASSESSMENTS																																	
Serum pregnancy test[h]	X	X																					X										
Coagulation	X	X										X	X	X	X	X						X	X			X	X		X	X		X	X
Hematology, Chemistry	X	X										X	X	X	X	X						X	X			X	X		X	X		X	X
Urinalysis	X	X										X	X	X	X	X						X	X			X	X		X	X		X	X
Hepatitis serology, HIV	X																																
Anti-AMG 211-antibody		X																			X									X		X	X
DOSING																																	
AMG 211										X																	X						
TUMOR ASSESSMENTS																																	
MRI or CT	X[e]																														X[f]		X[j]
Tumor markers (eg, CEA)	X	X																				X									X[f]		
BIOMARKER ASSESSMENTS																																	
Circulating tumor cells	X	X														X															X[f]	X	X
Immune cells	X	X					X					X	X	X		X							X[e]			X[e]	X[e]	X[e]	X[e]			X	X
Soluble DNA markers	X	X		X			X					X	X	X		X							X[e]			X[e]	X[e]	X[e]	X[e]		X[f]	X	X
Serum markers		X					X					X	X	X									X[e]			X[e]	X[e]	X[e]					
Archival tumor tissue	X																																
Tumor biopsy[b]	X													X																			
PK ASSESSMENTS																																	
AMG 211 PK collection		X		X			X					X	X	X		X	X	X	X	X	X					X[e]	X[e]			X[e]			
sCEA	X	X		X			X					X	X	X		X										X[e]	X[e]			X[e]			

With:

Additional tumor markers and tumor biopsy assessments

	SCR	Treatment Period																															
Cycle		1																					2 and all subsequent cycles[k]								Q2C	EOIP	EOS
Study Day	-21 to - 1	1										2	3-5	8	11	15					16	22	1			2	3-5	8	15	22			
Hours			Relative to start of infusion													Relative to EOI								Relative to start of infusion									
		Pre-dose	0-1.5	2	3	4	6	8	12	14	20	24	48-96	168		EOI	0.5	2	4	8	24		Pre-dose	0	6	24	48-96	168	336				
GENERAL ASSESSMENTS																																	
Informed consent	X																																
Hospitalization							X[c]																		X[c]								
Concomitant medications	X	X	→																												→	X	X
Adverse events	X	X	→																												→	X	X
Clinical evaluation[a]	X	X										X	X	X	X	X					X	X	X			X	X	X	X	X		X	X
Vital signs, pulse oximetry	X	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		X[i]	X	X	X	X	X		X	X
12-lead ECG (triplicate measurement)	X	X										X				X						X	X[e]			X[e]				X[e]			X
LABORATORY ASSESSMENTS																																	
Serum pregnancy test[h]	X	X																					X										
Coagulation	X	X										X	X	X	X	X						X	X			X	X		X	X		X	X
Hematology, Chemistry	X	X										X	X	X	X	X						X	X			X	X		X	X		X	X
Urinalysis	X	X										X	X	X	X	X						X	X			X	X		X	X		X	X
Hepatitis serology, HIV	X																																
Anti-AMG 211-antibody		X																			X									X		X	X
DOSING																																	
AMG 211										X																	X						
TUMOR ASSESSMENTS																																	
MRI or CT	X[g]																														X[f]		X[j]
Tumor markers (eg, CEA)	X	X																			**X**		**X**						**X**			**X**	**X**
BIOMARKER ASSESSMENTS																																	
Circulating tumor cells	X	X														X															X[f]	X	X
Immune cells	X	X					X					X	X	X		X							X[e]			X[e]	X[e]	X[e]	X[e]			X	X
Soluble DNA markers	X	X		X			X					X	X	X		X							X[e]			X[e]	X[e]	X[e]	X[e]		X[f]	X	X
Serum markers		X					X					X	X	X									X[e]			X[e]	X[e]	X[e]					
Archival tumor tissue	X																																
Tumor biopsy[b]	X													X[l]														**X[l]**					
PK ASSESSMENTS																																	
AMG 211 PK collection		X		X			X					X	X	X		X	X	X	X	X	X					X[e]	X[e]		X[e]				
sCEA	X	X		X			X					X	X	X		X										X[e]	X[e]		X[e]				

With:

Replace:

In the footnote:

EOT = End of Treatment

With:

*EO**IP** = End of **Investigational Product***

Replace:

[b] Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8) and/or an optional on-treatment biopsy at cycle 1 day 8.

With:

*[b] Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8 **to 14**) and/or an optional on-treatment biopsy at cycle 1 day 8 **to 14**.*

Replace:

[e] Obtained at cycle 2, 4 and 6 or 8 only.

With:

*[e] Obtained at cycle 2, 4, **6 and** 8 only.*

Add:

In the footnote:

[l] One optional tumor biopsy may be provided at cycle 1 after the first or second week of treatment with AMG211, and a separate optional biopsy may be provided at cycle 2 or a subsequent cycle after the first or second week of treatment with AMG211.

Section: 7.1, Table 8

Replace:

	SCR	Treatment Period																																				
Cycle		1																																2 and all subsequent cycles[i]						
Study Day	-14 to -1[k]	1									2	3-5	8	11	15	18	22	25	29					30	36	1			2	3-5	8	15	22	29	36			
Hours		Pre-dose	Relative to start of infusion																Relative to EOI							Pre-dose	Relative to start of infusion												
			0-1.5	2	3	4	6	8	12	14	20	24	48-96	168					EOI	0.5	2	4	8	24			0	6	24	48-96	168	336							
GENERAL ASSESSMENTS																																						
Informed consent	X																																					
Hospitalization							X[c]																					X[c]											
Concomitant medications	X	X	→																																			
Adverse events	X	X	→																																			
Clinical evaluation[a]	X	X									X	X	X	X	X	X	X	X	X					X	X	X			X	X	X	X	X	X	X			
Vital signs, pulse oximetry	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		X[c]	X	X	X	X	X	X	X			
12-lead ECG (triplicate measurement)	X	X									X								X						X	X[e]			X[e]						X[e]		
LABORATORY ASSESSMENTS																																						
Serum pregnancy test[a]	X	X																								X												
Coagulation	X	X									X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X			
Hematology, Chemistry	X	X									X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X			
Urinalysis	X	X									X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X			
Hepatitis serology, HIV	X																																					
Anti-AMG 211-antibody		X																						X													X	
DOSING																																						
AMG 211											X																												
TUMOR ASSESSMENTS																																						
MRI or CT	X[f]																																					
Tumor markers (eg, CEA)	X	X																	X																			
BIOMARKER ASSESSMENTS																																						
Circulating tumor cells	X	X													X				X																			
Immune cells	X	X					X				X	X	X		X		X		X							X[e]			X[e]	X[e]	X[e]	X[e]		X[e]			
Soluble DNA markers	X	X		X			X				X	X	X		X		X		X							X[e]			X[e]	X[e]	X[e]	X[e]					
Serum markers		X					X				X	X	X													X[e]			X[e]	X[e]	X[e]						
Archival tumor tissue	X																																					
Tumor biopsy[a]	X												X																									
PK ASSESSMENTS																																						
AMG 211 PK collection		X		X			X				X	X	X		X				X	X	X	X	X	X					X[e]	X[e]		X[e]		X[e]			
sCEA	X	X		X			X				X	X	X		X				X										X[e]	X[e]		X[e]		X[e]			

With:

Additional tumor markers and tumor biopsy assessments

	SCR	Treatment Period																																		
Cycle		**1**																								**2 and all subsequent cycles[i]**										
Study Day	**-21 to -1**	**1**									**2**	**3-5**	**8**	**11**	**15**	**18**	**22**	**25**	**29**					**30**	**36**	**1**			**2**	**3-5**	**8**	**15**	**22**	**29**	**36**		
Hours		Pre-dose	Relative to start of infusion																Relative to EOI							Pre-dose	Relative to start of infusion									
			0-1.5	2	3	4	6	8	12	14	20	24	48-96	168					EOI	0.5	2	4	8	24			0	6	24	48-96	168	336					
GENERAL ASSESSMENTS																																				
Informed consent	X																																			
Hospitalization							X[c]																				X[c]									
Concomitant medications	X	X	→																																	
Adverse events	X	X	→																																	
Clinical evaluation[a]	X	X									X	X	X	X	X	X	X	X	X					X	X	X			X	X	X	X	X	X	X	X
Vital signs, pulse oximetry	X	X	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X	X	X		X[c]	X	X	X	X	X	X	X	X
12-lead ECG (triplicate measurement)	X	X									X								X						X	X[c]			X[c]							**X[c]**
LABORATORY ASSESSMENTS																																				
Serum pregnancy test[d]	X	X																								X										
Coagulation	X	X									X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X	X
Hematology, Chemistry	X	X									X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X	X
Urinalysis	X	X									X	X	X	X	X	X	X	X	X						X	X			X	X		X	X	X	X	X
Hepatitis serology, HIV	X																																			
Anti-AMG 211-antibody		X																						X												
DOSING																																				
AMG 211			X																								X									
TUMOR ASSESSMENTS																																				
MRI or CT	X[f]																																			
Tumor markers (eg, CEA)	X	X																	X							**X**									**X**	
BIOMARKER ASSESSMENTS																																				
Circulating tumor cells	X	X													X				X																	
Immune cells	X	X					X				X	X	X		X		X		X							X[e]			X[e]	X[e]	X[e]	X[e]		X[e]	
Soluble DNA markers	X	X		X			X				X	X	X		X		X		X							X[e]			X[e]	X[e]	X[e]	X[e]			
Serum markers		X					X				X	X	X													X[e]			X[e]	X[e]	X[e]				
Archival tumor tissue	X																																			
Tumor biopsy[b]	X												X[c]																		X[c]					
PK ASSESSMENTS																																				
AMG 211 PK collection		X		X			X				X	X	X		X				X	X	X	X	X	X					X[e]	X[e]		X[e]		X[e]	
sCEA	X	X		X			X				X	X	X		X				X										X[e]	X[e]		X[e]		X[e]	

Replace:

In the footnote:

[a] EOT = End of Treatment

With:

*EO**IP** = End of **Investigational Product***

Replace:

[e] Obtained at cycle 2, 4 and 6 or 8 only.

With:

[e] *Obtained at cycle 2, 4, **6 and 8** only.*

Add:

In the footnote:

[k] One optional tumor biopsy may be provided at cycle 1 after the first or second week of treatment with AMG211, and a separate optional biopsy may be provided at cycle 2 or a subsequent cycle after the first or second week of treatment with AMG211.

Section: 7.1, Table 8

Replace:

	Treatment Period		
Cycle	Q2C	EOT	EOS
Study Day			
Hours			
TUMOR ASSESSMENTS			
MRI or CT	X[i]		X[i]
Tumor markers (eg, CEA)	X[i]		

With:

	Treatment Period		
Cycle	Q2C	EO**IP**	EOS
Study Day			
Hours			
TUMOR ASSESSMENTS			
MRI or CT	X[i]		X[i]
Tumor markers (eg, CEA)		**X**	**X**

Replace:

In the footnote:

EOT = End of Treatment

With:

*EO**IP** = End of **Investigational Product***

Replace:

[b] If a core biopsy is performed, it must be completed before the start of treatment. Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8) and/or an optional on-treatment biopsy at cycle 1 day 8.

With:

b If a core biopsy is performed, it must be completed before the start of treatment. Subjects who provide a separate consent may undergo an optional paired biopsy (1-2 weeks prior to cycle 1 day 1 and cycle 1 day 8 to 28) and/or an optional on-treatment biopsy at cycle 1 day 8 to 28.

Section: 7.2.3 End of Investigational Product (EOIP)

Replace title section:

7.2.3 End of Treatment

With:

*7.2.3 End of **Investigational Product (EOIP)***

Replace:

The EOT visit will occur upon documented confirmed clinical or radiographic disease progression, intolerable adverse event, or withdrawal of consent. For subjects who choose to discontinue investigational product treatment, the EOT visit should occur as soon as possible after the last dose of investigational product is administered. Medically

significant adverse events, considered related to the investigational product by the investigator or the sponsor, will be followed until resolved or considered stable. The following procedures will be completed during the EOT visit as designated in the Schedules of Assessments (Table 6, Table 7, and Table 8).

With:

*The **EOIP** visit will occur upon documented confirmed clinical or radiographic disease progression, intolerable adverse event, or withdrawal of consent. For subjects who choose to discontinue investigational product treatment, the **EOIP** visit should occur as soon as possible after the last dose of investigational product is administered. Medically significant adverse events, considered related to the investigational product by the investigator or the sponsor, will be followed until resolved or considered stable. The following procedures will be completed during the **EOIP** visit as designated in the Schedules of Assessments (Table 6, Table 7, and Table 8).*

Add:

- ***Tumor markers***

Section: 7.2.4 End of Study (EOS) Visit

Replace title section:

7.2.4 End of Study

With:

*7.2.4 End of Study **(EOS)** Visit*

Add:

- ***Tumor markers***

Section: 7.3.8 Tumor Biopsy

Replace:

Subjects in the 14-day or 28-day infusion cohorts who provide a separate consent may also undergo an optional on-treatment biopsy (cycle 1 day 8).

With:

*Subjects in the 14-day or 28-day infusion cohorts **may also** provide a separate consent **to** undergo **one or two** optional on-treatment biopsi**es**:*

- ***One biopsy on cycle 1 after the first or second week of treatment with AMG211.***
- ***One biopsy provided in cycle 2 or subsequent cycles after the first or second week of treatment with AMG 211.***

Section: 7.3.12.1 Serum Pregnancy Test

Replace:

A serum pregnancy test will be performed locally at each site on all females unless they are surgically sterile or ≥ 2 years postmenopausal. On visits where required, the serum pregnancy test must be performed prior to dosing with investigational product. If the pregnancy test is positive at day 1 of cycle 1, the subject should not be given investigational product. If the pregnancy test is positive at any other visit, then investigational product must be discontinued and the subject should be removed from the study.

With:

*A serum **qualitative** pregnancy test will be performed locally at each site on all females unless they are surgically sterile or ≥ 2 years postmenopausal. On visits where required, the serum pregnancy test must be performed prior to dosing with investigational product. If the pregnancy test is positive at day 1 of cycle 1, the subject should not be given investigational product. If the pregnancy test is positive at any other visit, then investigational product must be **held and a confirmatory quantitative serum pregnancy test must be done. If the confirmatory quantitative serum pregnancy test is positive, the investigational product (AMG 211) must be discontinued. If the quantitative pregnancy test is negative the subject should re-start infusion per the criteria in section 6.2.1.4.3.***

Section: 7.4 Antibody Testing Procedures

Replace:

Additional blood samples may be obtained to rule out anti-AMG 211 antibodies during the study.

With:

*Additional blood samples may be obtained to **evaluate** anti-AMG 211 antibodies' **impact on AMG 211 exposure** during the study.*

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

Add:

Subject data and the reason(s) for termination or withdrawal from the study must be documented for the final study CSR, and it may be used for the analysis of the study.

Section: 9.1.1 Definition of Adverse Events

Replace:

For situations when an adverse event or serious adverse event is due to the primary tumor type being studied, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). If a new primary malignancy appears, it will be considered an adverse event.

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

With:

Disease progression itself is not considered an adverse event; however, signs and symptoms of disease progression should be recorded as adverse events or serious adverse events. Deaths due to progressive disease during treatment until the Safety Follow-up Visit or 30 days after the protocol specified therapy, whichever is later, should be recorded as due to the primary tumor *(eg, metastatic pancreatic cancer). If a new primary malignancy appears, it will be considered an adverse event.*

Add:

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not 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.

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Delete:

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) should be recorded as the adverse events.

Section: 10.1.1 Study Endpoints, Primary Endpoints

Replace:

Safety: subject incidence of AEs, DLTs, and clinically significant changes in vital signs, ECGs, physical examination findings, and clinical laboratory tests

With:

Safety: subject incidence of **TEAEs**, DLTs, and clinically significant changes in vital signs, ECGs, physical examination findings, and clinical laboratory tests

Section: 10.1.1 Study Endpoints, Secondary Endpoints

Replace:

- PK of AMG 211 after cIV infusion across 2 cycles
- Time to progression

With:

- *PK of AMG 211 after **continuous intravenous (cIV)** infusion across 2 cycles*
- *Time to progression **(TTP)***

Section: 10.1.1 Study Endpoints, Exploratory Endpoints

Replace:

- Changes in CTCs
- sCEA serum levels

With:

- *Changes in **circulating tumor cells** (CTCs)*
- ***Soluble** CEA serum levels*

Section: 10.2 Sample Size Considerations

Replace:

It is anticipated that up to 78 subjects will be enrolled in this study.

With:

*It is anticipated that **approximately** 78 subjects will be enrolled in this study.*

Section: 10.3 Planned Analysis

Replace:

The following data analyses are planned: (1) dose decision analyses in the dose-escalation cohorts after every 3 DLT-evaluable subjects, (2) a safety review of dose escalation after all subjects in dose escalation have had the opportunity to complete 6 months of treatment, (3) the primary analysis after all dose-escalation and dose-expansion subjects have completed 6 months of treatment, and (4) the final analysis after all subjects have ended the study.

With:

*The following data analyses are planned: (1) dose decision analyses in the dose-escalation cohorts after every 3 **to 6** DLT-evaluable subjects, (2) a safety review of dose escalation after all subjects in dose escalation have had the opportunity to complete 6 months of treatment, (3) the primary analysis after all dose-escalation and dose-expansion subjects have completed 6 months of treatment, and (4) the final analysis after all subjects have ended the study.*

Section: 10.3.1 Interim Analysis

Replace:

The Amgen Medical Monitor and Amgen Global Safety Officer may decide to open the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated by the DLRT.

With:

*The Amgen Medical Monitor (**or EDL)** and Amgen Global Safety Officer may decide to open the next cohort using a de-escalated dose (de-escalated from the dose level of the most recent cohort), if this de-escalated dose had been previously evaluated by the DLRT.*

Section: 10.3.2 Dose Level Review Team

Replace:

All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory results, and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria (including hematologic) will be reviewed and can be considered in the DLRT's decisions.

With:

All available study data, including demographics, investigational product administration, medical history, concomitant medications, ***prior surgery and therapy****, adverse events, ECGs, vital signs, laboratory results,* ***Karnofsky Performance Status, Glomerular Filtration Rate (GFR), Cancer Diagnosis*** *and PK/PD information will be reviewed. In addition to DLTs, all ≥ grade 3 toxicities not meeting DLT criteria (including hematologic) will be reviewed and can be considered in the DLRT's decisions.*

Section: 10.3.3 Safety Review

Add Section ***10.3.3 Safety Review***

The safety review is planned after all dose-escalation subjects have had the opportunity to complete 6 months of treatment.

Section: 10.3.4 Primary Analysis

Replace:

The primary analysis is planned after all subjects have had the opportunity to complete 6 months of treatment.

With:

The primary analysis is planned after all ***dose-escalation and dose-expansion*** *subjects have had the opportunity to complete 6 months of treatment.*

Section: 10.4.2.1.1 Adverse Events

Replace:

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.

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.

With:

*Subject incidence of all treatment-emergent adverse events **(TEAEs)** will be tabulated by system organ class **(SOC)** and preferred term **(PT).** The number and percentage of subjects reporting adverse events will be evaluated overall and by dose level and will also be tabulated by relationship to study drug.*

*Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies and **Events of Interest (EOI)** will also be provided.*

Section: 10.4.2.1.2 Clinical Laboratory Tests

Replace:

The analysis of safety laboratory endpoints will include summary statistics over time for each subject. Shifts in grade of safety laboratory values from baseline will be tabulated for each subject.

With:

The analysis of safety laboratory endpoints will include summary statistics over time for each subject. Shifts in grade of safety laboratory values from baseline will also be tabulated.

Section: 10.4.3.1 Pharmacokinetics Data Analysis

Replace:

Parameters will be summarized by dose level using means, standard deviations, medians, minimums, and maximums. PK/PD modeling may be performed if data are adequate to explore the relationship between AMG 211 exposure and various PD endpoints.

With:

*Parameters will be summarized by dose level and **each sampling time** using means, standard deviations, medians and **ranges**. PK/PD modeling may be performed if data are adequate to explore the relationship between AMG 211 exposure and various PD endpoints.*

Section: 10.4.3.3 Efficacy Parameter Analysis

Delete:

Statistical analyses of efficacy endpoints will be considered exploratory.

Section: 13 REFERENCES

Delete:

MedImmune. MEDI-565

Add:

Investigator's Brochure, version 5.0; dated 03 March 2014.

Michael J. Pishvaian, Michael Morse, Jennifer T. McDevitt, Song Ren, Gabriel Robbie, Patricia C. Ryan, Serguei Soukharev, Haifeng Bao, Crystal Shereen Denlinger; Phase 1 dose escalation study of MEDI-565, a bispecific T-cell engager that targets human carcinoembryonic antigen (CEA), in patients with advanced gastrointestinal (GI) adenocarcinomas. J Clin Oncol 34, 2016 (suppl 4S; abstr 320+poster).

Section: Appendix C.

Change: ***Pregnancy and Lactation Notifications worksheets updated with latest Amgen versions***

Amendment #2

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 211 Administered as Continuous Intravenous Infusion in Subjects With Relapsed/Refractory Gastrointestinal Adenocarcinoma

Amgen Protocol Number (AMG 211) 20130354

EudraCT Number 2014-000201-12

Amendment Date: 03 September 2015

Rationale:

The protocol was amended for the following reasons:

- Incorporate language regarding subjects being allowed to concurrently participate in the 20130354 study and the study sponsored by the University Medical Center Groningen and conducted in the Netherlands, referred to as the Imaging Study. The Imaging Study will be conducted following a separate protocol and its objective is to evaluate the accumulation and distribution of a radio-labelled version of AMG 211. Assessments and treatment in the 20130354 study will be independent the Imaging Study.
- Increase sample size from 34 to 78 subjects to ensure recommended phase 2 dose can be established and sufficient clinical and safety data can be obtained.
- Screening period increased from 14 days to 21 days to allow sufficient time for all assessments to be completed.
- Allow start of treatment at cycle 2 and all subsequent cycles +1 day outside established window if justified for logistical reasons.
- The schedule of assessments table was updated to include imaging assessment at EOS if not done within the previous 6 weeks. This is not an additional assessment as it would be in line with the Q2C (every 2 cycles) requirements in the previous version of the protocol.
- The schedule of assessments table was corrected with PK and sCEA samples to be collected on cycle 2 (and all subsequent cycles) at D15 instead of D22. This is in accordance to the protocol language which says that these samples should be collected at the end of infusion.
- Correction of AMG 211 volume contained in vial.
- Collection of tumor tissue obtained as a result of a non-study related surgery or any invasive procedure
- Administrative, typographical and formatting changes were made throughout the protocol.

Amendment 1

Protocol Title: A Phase 1 Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 211 Administered as Continuous Intravenous Infusion in Subjects with Relapsed/Refractory Gastrointestinal Adenocarcinoma

Amgen Protocol Number (AMG 211) 20130354

EudraCT Number 2014-000201-12

Amendment Date: 29 July 2014

Rationale:

The following changes were made to protocol 20130354, dated 24 March 2014, with this amendment:

- The preferred imaging methodology is being updated to indicate that a contrast-enhanced MRI should be the preferred imaging method for evaluation of most tumors in order to reduce radiation exposure for subjects as requested by Ethics Committees. However, organ-specific existing imaging protocols or existing diagnostic guidelines should be followed whenever possible to evaluate the extent of the disease appropriately. Specifically for the chest a contrast-enhanced MRI may not yield image quality sufficient for a convincing evaluation within an acceptable examination time (e.g. evaluation of the lung parenchyma for small nodules below 10 mm nodules, to differentiate between malignant and benign nodules and where MRI is prone to have more motion artifacts) and is therefore currently not recommended for TNM Classification of Malignant Tumours by Union for International Cancer Control (UICC) and International Association for the Study of Lung Cancer (IASLC) criteria.
  The radiation exposure for a CT scan of a single body area is lower in comparison to a complete tumor assessment by imaging with CT (e.g. for chest CT 1.5 - 7 mSv per scan depending on technique, size of scanned area and

scanning time versus approximately 17 mSv for CT scans of abdomen, pelvis and chest).

An exact tumor evaluation is of high importance for subjects with advanced tumors including those participating in early phase clinical trials. These subjects per se have a poor prognosis and are at high risk to suffer from toxicity. Consequently, a thorough and accurate tumor assessment has to guide the investigator in their decision to continue or to discontinue treatment depending on the risk-benefit for an individual subject.

We are proposing the revised language in the study protocol recognizing the need to reduce radiation exposure in subjects while balancing the ability to adequately assess tumor burden and sites of disease.

- Language added to clarify the timing of the confirmatory scans per feedback from the German Regulatory Authority.
- Section 6.2.1.2 was updated to include a more precise description of the safety monitoring procedures in the outpatient setting. Specifically, the possibility for site personnel instead of the Home Health Care Personnel to contact the subject by telephone on the days that the subject is not hospitalized was added. In addition, the measurement of the subject's vital signs during the visits at the subject's home by the Home Health Care Personnel/Study Personnel was added for safety purposes.
- The collection of an unscheduled blood sample was added in sections 6.5 and 7.3.12 to measure and confirm cytokine levels in case of the occurrence of cytokine-release associated adverse events.
- The collection of vital signs and pulse oximetry every 6 hours during day 1 of cycle 2 and all subsequent cycles was added per feedback from the German Regulatory Authority to ensure that subjects are monitored while hospitalized.
- The collection of a sample for soluble DNA markers was added to the screening visit as two pre-treatment values are needed for the analysis of this biomarker.
- Exclusion criterion 4.2.9 was updated per feedback from the German Regulatory Authority to differentiate prophylactic anti-infection vaccination and therapeutic vaccination and respective time windows between the start of treatment and prior vaccination.
- Exclusion criterion 4.2.11 was corrected as it was a typographic error and requested by German Ethics Committee.

- Exclusion criterion 4.2.16 was updated per feedback from the German Regulatory Authority to clarify and specifically exclude subjects with inflammatory bowel disease.
- A typographic error was corrected regarding the description of the vial size of the IV Bag Protectant given in the protocol as it was wrongly described as 20 mL instead of the correct size of 20 mm. In addition, the amount of IV bag protectant present in the vial was added.

Description of Changes:

Section: Global

Replace: The version is updated to Amendment 1 and the date is updated to 29 July 2014

Section: Global

Change: The preference for MRI scans was reflected throughout the complete protocol document by changing to "**MRI or CT**" instead of "CT or MRI".

Section: Protocol Synopsis, Amgen Investigational Product Dosage and Administration, line 3

Replace:

The intravenous (IV) bag protectant will be presented as a sterile liquid in a 20 mL glass vial intended for pre-treatment of IV bags prior to dilution of AMG 211 drug product.

With:

The intravenous (IV) bag protectant will be presented as a sterile liquid in a 20 **mm** glass vial **(containing 10 mL of IV bag protectant)** intended for pre-treatment of IV bags prior to dilution of AMG 211 drug product.