Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 as Monotherapy and in Combination With AMG 404 in Subjects With Glioblastoma or Malignant Glioma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

AMG 596

Amgen Protocol Number 20160132

IND Number 134352

EudraCT number 2017-001658-32

Clinical Study Sponsor:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320
Phone: +1 805-447-1000

Key Sponsor Contact(s):

, PhD
Early Development Lead
Phone:
Email:

, PhD
Clinical Research Study Manager
Phone
Email:

Date:	28 April 2017
Amendment 1 Date:	05 July 2017
Amendment 2 Date:	30 January 2018
Amendment 3 Date:	17 May 2018
Amendment 4 Date:	11 March 2019
Amendment 5 Date:	29 July 2019

NCT Number: NCT03296696
This NCT number has been applied to the document
for the purposes of posting on clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled, "Phase 1 [redacted] Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 as Monotherapy and in Combination with AMG 404 in Subjects with Glioblastoma or Malignant Glioma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII) dated 29 July 2019, and agree to abide by all provisions set forth therein.

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

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

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

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

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 as Monotherapy and in Combination with AMG 404 in Subjects with Glioblastoma or Malignant Glioma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Study Phase: *1*

Indication: EGFRvIII-positive glioblastoma (GBM) or malignant glioma after recurrence or as maintenance after Standard of Care (SoC) treatment in newly diagnosed subjects

Primary Objective:

Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion in monotherapy (Arm 1) and in combination with AMG 404 (anti-programmed cell death-1 (PD-1) antibody (Arm 2) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and in the maintenance treatment phase of newly diagnosed glioblastoma (maintenance setting Group 2)

Secondary Objective(s):

- Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion either in monotherapy or in combination with AMG 404
- Evaluate the pharmacokinetics (PK) of AMG 404 in serum when administered by short term infusion in combination with AMG 596
- Evaluate the clinical benefit of AMG 596 and AMG 596 in combination with AMG 404 as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent and in the maintenance setting
- Evaluate progression free survival (PFS) at 6 and 12 months after initiation of treatment for any Part, Arm and Group of the study

Exploratory Objective(s):

[redacted]

Hypotheses:

- AMG 596 monotherapy and in combination with AMG 404 are safe and well tolerated in at least one dose level when administered in subjects with EGFRvIII-positive glioblastoma, or malignant glioma in the recurrent (Group 1) and in the maintenance setting (Group 2)
- AMG 596 monotherapy and/or AMG 596 in combination with AMG 404 can induce objective tumor shrinkage and/or overcome lack of response to SoC in subjects with EGFRvIII-positive glioblastoma or malignant glioma in either recurrent or in the maintenance setting at a tolerable dose.

Primary Endpoint:

- Dose limiting toxicities (DLT), treatment-emergent adverse events, treatment-related adverse events and changes in vital signs, physical examinations, and clinical laboratory tests

- **Secondary Endpoint(s):** PK parameters for AMG 596 including, but not limited to, average steady-state concentration (C_{ss}), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life ($t_{1/2}$) for serum AMG 596
- PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (C_{max}), time to achieve C_{max} (t_{max}) and AUC.
- PK parameters for AMG 596 dosed in combination with AMG 404 including, but not limited to, average steady-state concentration (C_{ss}), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life ($t_{1/2}$) for serum AMG 596
- Objective response (OR) as per modified RANO, time to response, response duration and time to progression (TTP); progression free survival (PFS) at 6 and 12 months after treatment initiation with AMG 596 monotherapy or AMG 596 in combination with AMG 404

- **Exploratory Endpoint(s):** [redacted]

Study Design:

This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma exploring of AMG 596 monotherapy (Arm 1) and the combination of AMG 596 with AMG 404 (Arm 2). Both Arm 1 and Arm 2 consist of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). Both Arm 1 and Arm 2 will enroll 2 groups of subjects according to disease stage, recurrent disease (Group 1) and maintenance treatment after SoC in newly diagnosed disease (Group 2). *Part 1, Dose Escalation:* The purpose of dose escalation is to make a preliminary estimate of the Recommended Phase 2 Dose (RP2D)/ Maximum Tolerated Dose (MTD) of AMG 596 monotherapy and in combination with AMG 404. Treatment is divided into 2 periods: (1) DLT period 1 for [redacted] of AMG 596 infusion and (2) DLT period 2 for [redacted] of infusion (applies for both Arms). This distinction between DLT period 1 and DLT period 2 is maintained throughout dose escalation until the end of the dose escalation phase. Observations from other bispecific T-cell engager (BiTE®) studies have shown that the occurrence of initial non-cumulative toxicities associated with cytokine release within the first 48 hours after start of infusion may limit dose escalation resulting in the utilization of below doses assumed to be associated with anti-tumor activity. However, should the initial dose (DLT period 1) be limited by severe adverse events related to first dose effects (eg, cytokine release associated adverse events), an MTD for the first dose step may be defined. Further dose escalation in DLT period 2 is possible resulting in a step-dosing and a second (and higher) MTD. This approach supports the ongoing evaluation of initial toxicity, as well as after an MTD for the start dose has been defined.

The start dose based on preclinical evaluations for the estimation of the Minimum Anticipated Biological Effective Level (MABEL) is [redacted] µg/day.

Further pre-specified nominal AMG 596 doses for potential use in any dose escalation Arms are [redacted] µg/day. The dose level review team (DLRT) may consider treating at intermediate doses if required. If the MTD or a biological active dose considered the RP2D is not reached within the pre-planned nominal dose range, the DLRT may decide to expand the nominal dose range to dose levels [redacted] µg/day after careful consideration of all available safety, laboratory, and PK information. The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and separately in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2) and separately for AMG 596 monotherapy and in combination with AMG 404.

If the same AMG 596 doses are to be explored in monotherapy and in combination, the monotherapy cohort must be completed before enrollment in the combination cohort. In the multiple subject cohorts, a safety observation window of at least 72 hours must apply between

start of subjects 1, 2 and 3 of each dose escalation cohort. Intra-subject dose escalation will be allowed to higher AMG 596 dose levels in subsequent treatment cycles once a higher dose has been deemed safe by the DLRT. Subjects who do not proceed to a higher dose may continue at the original dose.

Group 1, Recurrent Disease

- *Dose Escalation in single subject cohorts:*
  - In first cohorts AMG 596 will be administered as a cIV infusion for [redacted] at escalating doses with N=1 per cohort. In the single subject cohorts, only a limited number of subjects will be enrolled at dose levels anticipated to be lower than those at which visible pharmacodynamics activity including adverse events related to AMG 596 therapy will be expected. In addition, the investigator together with the subject will decide on subsequent treatment duration carefully. Subjects are allowed to stay on study in [redacted] cycles until discontinuation criteria apply.
  - Combination of AMG 596 and AMG 404: The starting dose of AMG 596 is [redacted] ug/day administered in [redacted] cycles and the defined AMG 404 dose is [redacted] mg every 4 weeks.
  - The cohort size will be increased to N=2-4 subjects (ie, Start of multiple subject cohorts) after observation of
    - Treatment-related adverse events of common terminology criteria for adverse events (CTCAE 4.0) grade 2 or higher and/or
    - Quantifiable cytokine levels in blood or CSF above baseline
- *Dose Escalation in multiple subject cohorts:*
  - Subjects in the first multiple subject cohort receive the same dose as the last single subject cohort
  - All subjects receive AMG 596 in [redacted] infusion cycles until treatment discontinuation criteria apply.

  It is anticipated that dose-escalation will proceed according to the pre-planned nominal doses though intermediate dose levels may be used if required after reviewing all available safety data. When a first DLT is observed, the Bayesian logistic regression model (BLRM) will be used to guide dose level selection (Neuenschwander et al., 2008). The cohort size will be N=2-4 subjects. On a limited basis, after agreement between the investigator and medical monitor, one additional subject may be allowed to be enrolled if the subject has been determined to be eligible and the cohort has been filled. In this case, all five subjects will be reviewed and assessed in the Dose Level Review Meeting (DLRM). After each cohort, the model's recommended MTD dose level for evaluation is the dose level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.25 probability of an excessive or unacceptable TPI. The target TPI is (0.20, 0.33], and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the DLRT after considering all information. Dose escalation will be completed when any of the following occurs:

  - The maximum total sample size of N=45 DLT evaluable subjects (including single subject cohorts) is reached for AMG 596 monotherapy and N=30 DLT evaluable subjects for AMG 596 in combination with AMG 404
  - The BLRM model recommends the same dose level at least 2 times and that at least 6 subjects have been treated at the recommended RP2D/MTD dose level. If step -dosing is required, this stopping criterion applies separately to each period.
  - The highest planned dose level is reached without any DLTs being observed

Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease

- A first cohort will start after observation of a first objective anti-tumor response in Group 1 subjects with recurrent EGFRvIII-positive glioblastoma or malignant glioma. The starting dose of AMG 596 monotherapy in Group 2 will be decided by DLRT and will be the current highest dose deemed safe of Group 1. Treatment may consist either of [redacted] dose AMG 596 cIV infusion or step-dosing as established for recurrent disease. Further treatment cycles with [redacted] between cIV infusions will be provided until any of the treatment discontinuation criteria applies.
- The starting dose of AMG 596 in combination with AMG 404 for Group 2 will be one dose level below the selected start dose for AMG 596 monotherapy and an AMG 404 dose of [redacted] mg.
- The BLRM will be used to guide dose level selection. The cohort size will be N=2-4 subjects. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the DLRT after considering all information.
- Dose escalation in Group 2 will be completed when any of the following occurs.
  - The maximum sample size of N=15 DLT evaluable subjects is reached for AMG 596 monotherapy or N=20 DLT evaluable subjects for the AMG 596 in combination with AMG 404.
  - At least 6 subjects have been treated at the recommended RP2D/MTD dose level
  - The highest pre-specified nominal dose level is reached without any DLTs being observed

Part 2: Dose Expansion

The purpose of dose expansion will be to further explore safety and to evaluate preliminary antitumor activity in subjects with recurrent disease (Group 1) and in subjects in the maintenance setting (Group 2). It is anticipated that 15 subjects will be enrolled to Group 1 and up to 25 subjects will be enrolled to Group 2.

In Group 2 (maintenance setting), the objective response rate (ORR) of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. The ORR in Group 2 will be evaluated after 10 subjects are treated and have been evaluated at the first on study imaging scan or have discontinued the study before that. If ORR is lower than 5%, enrollment may be terminated due to futility. Otherwise, the ORR will be evaluated for additional new subjects and the futility stopping rules are calculated using a Bayesian predictive probability design (see Section 10.2. for details).

A BLRM design may be used to update the estimate of the RP2D/MTD using data from subjects enrolled to dose escalation and dose expansion. Based on this revised RP2D/MTD estimate and reviewing all available safety data, the dose level for dose expansion may be revised.

The subjects enrolled in Part 2 dose expansion will be followed for imaging evaluation until the earliest of: clinically significant disease progression, death, consent withdrawal, start of new anti-tumor therapies or 12 months after treatment initiation. Subjects who stopped treatment will be contacted for long term follow up for up to 12 months after treatment initiation.

Sample Size: It is anticipated that around 190 subjects will be enrolled in the study, up to 100 subjects will be enrolled to Arm 1 and up to 90 subjects will be enrolled to Arm 2. Enrollment for Arm 1 and Arm 2 will occur at 12 or more sites across US, Australia and Europe.

For Group 1 (recurrent disease), the following are the planned sample sizes.

- In dose escalation, up to 45 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 30 DLT-evaluable subjects to combination Arm 2
- In dose expansion, up to 15 subjects will be enrolled to monotherapy Arm 1 and up to 15 subjects to combination Arm 2.

For Group 2 (maintenance setting), the following are the planned sample sizes.

- In dose escalation, up to 15 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 20 DLT-evaluable subjects to combination Arm 2
- In dose expansion, up to 25 subjects will be enrolled to monotherapy Arm 1 and up to 25 subjects to combination Arm 2

The sample size in dose escalation is based on practical considerations and it is consistent with conventional oncology studies with the objective to identify the RP2D/MTD. With 2 subjects per cohort, there is a 19-56% probability of observing at least one DLT for a cohort if the true DLT rate is 10-33% and with 6 subjects per cohort, the probability is 47-91%.

For both Arm 1 and Arm 2, the sample size for Group 1 dose expansion is based on practical considerations. With 21 subjects treated at the respective Group 1 RP2D/MTD (6 from dose escalation and 15 from dose expansion), there is a 66% probability of observing an adverse event with 5% incidence rate. For an objective response rate (ORR) of 20%, the probability of observing the OR in at least 4 subjects would be 63%. The estimated ORR for 4 responses is 19% (exact 80% confidence interval (CI): 9%-35%).

For both Arm 1 and Arm 2, the sample size for Group 2 dose expansion is based on a Bayesian predictive probability design (Lee, 2008). In Group 2, the ORR of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. The maximum sample size is 31 subjects (6 from dose escalation and 25 from dose expansion). Futility will be assessed initially after treating 10 subjects have been evaluated at the first imaging scan or have dropped out before that and continuously for each additional subject afterwards. If ORR is lower than 5%, enrollment may be terminated due to futility. See Section 10.2 for early termination guideline details.

With this design, the probability of accepting the treatment is 0.05 (type I error) when ORR=5% and 0.8 (power) when ORR=20%. If the ORR is 5%, the probability of stopping the trial early at the interim with 10 evaluable subjects for futility is 60% and the expected additional subjects to be assessed in dose expansion is 9.6.

Investigational Product (IP)

Amgen Investigational Product Dosage and Administration: AMG 596, AMG 404 and the intravenous solution stabilizer (IVSS) will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

AMG 596 is supplied as a sterile, single-use, preservative-free concentrate for solution for infusion in a vial containing [redacted] mg/mL AMG 596. The drug product is formulated with 10 mM sodium acetate, 9% sucrose, 0.01% (w/v) polysorbate 80, pH 5.5. The final container is a 5cc glass vial and contains 1 mL deliverable volume of AMG 596.

AMG 404 is supplied in a 3 mL Type 1 glass tubing vial containing 1 mL deliverable volume of [redacted] mg/mL. The drug product is formulated with 10 mM acetate (sodium counterion), 9.0% (w/v) sucrose, 0.01% (w/v) polysorbate 80, pH 5.2 and will be prepared for IV administration by dilution.

IVSS is supplied in 10 mL single-use glass vials as a sterile, preservative-free, clear, colorless-to---slightly-yellow liquid concentrate. It consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7. The IVSS is intended to prevent adsorption of AMG 596 to surfaces of the infusion components.

AMG 596 solution for intravenous infusion will be prepared in bags for IV infusion and delivered through infusion lines using preprogrammed infusion pumps approved for use in the country in which the subject is undergoing treatment. The drug will be administered as a cIV infusion at a constant flow rate for [redacted] cycles or over [redacted] cycles, followed by a [redacted] infusion-free interval prior to the following treatment cycle, until confirmed disease progression. The start dose based on preclinical evaluations for the estimation of the MABEL is [redacted] µg per day. Further pre-planned dose levels are [redacted] µg per day; step-dosing can be introduced.

AMG 404 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment. AMG 404 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines. The drug will be administered as an IV infusion at a constant flow rate over 30 minutes every [redacted]

The RP2D/ MTD or highest tested dose per group will be administered in the dose-expansion cohorts.

Procedures: The pre-screening evaluation is optional and serves to pre-determine EGFRvIII -positivity. Pre-screening can start once written informed consent for pre-screening has been obtained. Up to 500 subjects with diagnosed glioblastoma or malignant glioma may undergo the pre-screening evaluation, which can be performed any time prior to signing consent for study participation. During pre-screening, a tissue and/or plasma or CSF sample obtained any time after initial diagnosis of glioblastoma or malignant glioma will be collected and tested by an appropriate In Vitro Diagnostic (IVD) assay(s) for EGFRvIII-positivity (further details on the screening assays are provided in Section 7.2.1). After EGFRvIII-positivity has been confirmed and prior to signing consent for study participation, the subject may still receive one or more antitumor-treatments. Subjects may also enter directly into the screening period without pre-screening.

All subjects will be hospitalized for the following periods:
Cycle 1:

- For the first [redacted] of AMG 596 monotherapy (Arm 1)
- For the first [redacted] of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on [redacted]
- For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2
- For additional 72 hours after AMG 596 step dose if necessary

Cycle 2 and all subsequent cycles:

- For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2
- For additional 72 hours after AMG 596 step dose if necessary.

Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator.

AMG 404 can be administered in an outpatient setting starting from cycle 1 [redacted] onwards. Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.

Restart of infusion should be performed in the clinic/hospital under the supervision of the investigator or designee and the subject should be hospitalized for a minimum of 24 hours when the infusion interruption meets the following criteria:

- associated to an AE, or
- interruption > 24 hours due to a pump related issue.

Dosing with AMG 596 or the combination of AMG 596 and AMG 404 can continue unless the subject becomes intolerant to investigational product, the signs and symptoms of clinical progression are evident as determined by the investigator, or the subject withdraws consent. Tumor evaluations by MRI will occur every 10 to 12 weeks from treatment initiation. Earlier assessments can be made if clinically indicated at the discretion of the investigator. Modified RANO criteria will be used allowing subjects to stay on study until discontinuation criteria are met. Upon discussion with the Sponsor, subjects may continue to receive treatment beyond

radiographic confirmation of progressive disease as long as they continue to derive clinical benefit and until further increase in tumor burden. For analyses purpose, date of progressive disease (PD) is the date of initial observed clinical or radiographic PD.

Assessments during the course of the study include: Clinical evaluation (physical examination, Eastern Cooperative Oncology Group [ECOG] status, height, and weight), vital signs, pulse oximetry, neurological evaluation, electrocardiogram (ECG) triplicate measurement, laboratory assessments (including serum pregnancy test, if applicable, coagulation, hematology, chemistry, urinalysis, hepatitis serology, human immunodeficiency virus (HIV) test, [redacted] For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Section 7.1 Schedule of Assessment.

Statistical Considerations:

A primary analysis will be performed for each group separately when target enrollment in Part 1 and Part 2 is complete and each subject either completes 6 months on study or withdraws from the study.

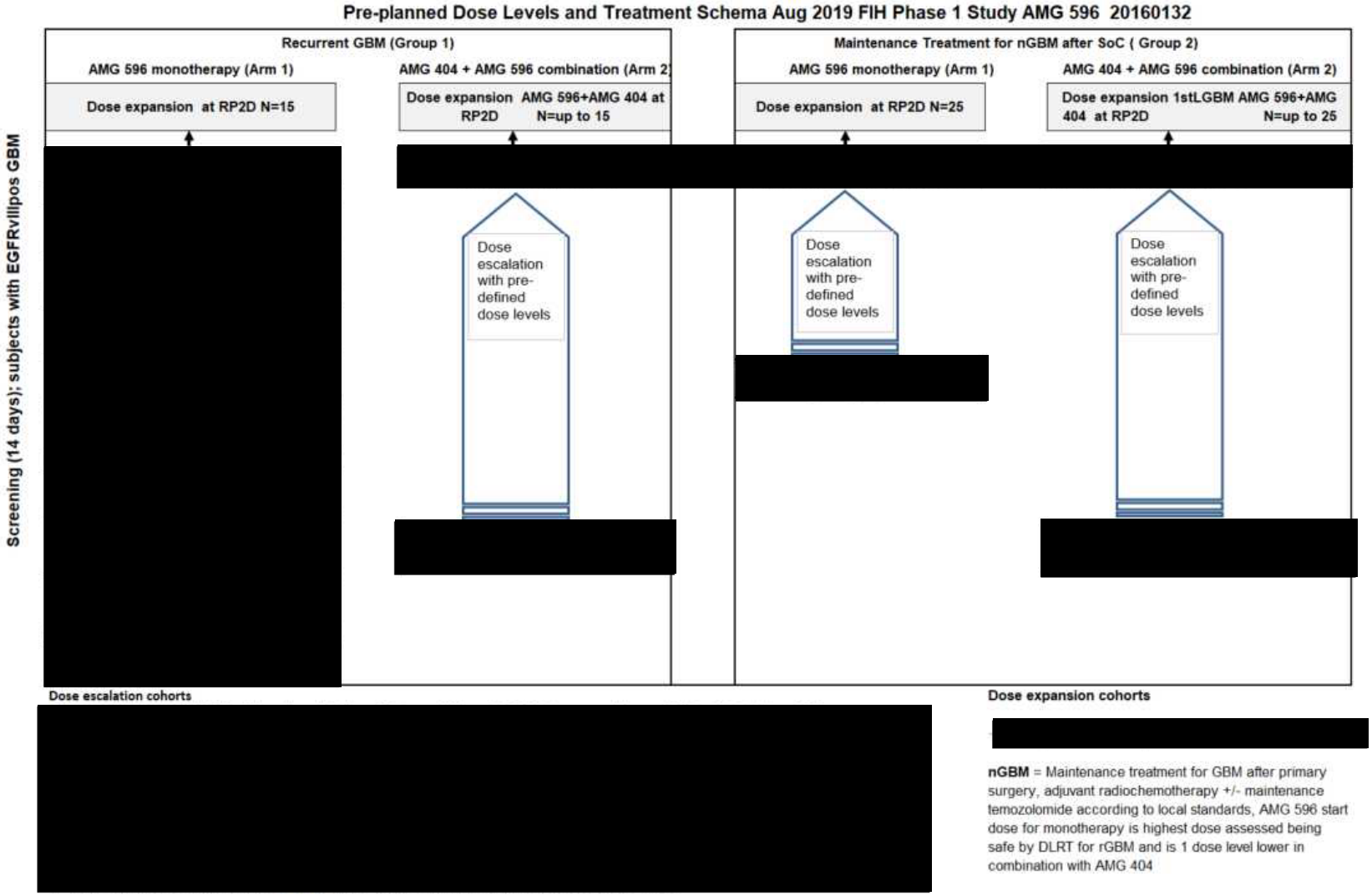
For both Arm 1 and Arm 2, in dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. For both Arm 1 and Arm 2, in dose expansion for Group 2, futility will be assessed initially for N=10 and continuously afterwards using a Bayesian predictive probability design.

Descriptive statistics will be provided for selected demographics, safety, PK, PD, efficacy and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. ORR will be presented with 80% Clopper-Pearson exact CI. PFS will be summarized using Kaplan-Meier (KM) method. Graphical summaries of the data may also be presented.

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

Sponsor: Amgen, Inc.

Figure 1. Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AE	Adverse event
[redacted]	
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMG 596	Anti EGFRvIII Bispecific T-cell Engager
ANA	Anti-nuclear antibody
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BiTE®	Bispecific T-cell engager
BLRM	Bayesian logistic regression model
CAR	Chimeric antigen receptor
CBC	Complete blood count
CEA	Carcinoembryonic antigen
[redacted]	
CI	Confidence interval
cIV	Continuous intravenous
CNS	Central nervous system
CPK	Creatine phosphokinase
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine-release syndrome
CSF	Cerebrospinal fluid
C_{max}	Maximum serum concentration
C_{ss}	Steady-state drug concentration in plasma during constant-rate infusion
CTCAE	Common terminology criteria for adverse events
d	Day
DILI	Drug induced liver injury
DLRM	Dose level review meeting
DLRT	Dose level review team
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DW	Diffusion-weighted
DWI	Diffusion-weighted imaging

Abbreviation or Term	Definition/Explanation
EC_{50}	50% of the maximal effective concentration level
EC_{90}	90% of the maximal effective concentration level
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ECOG	Eastern cooperative oncology group
EGF	Epidermal growth factor
EGFRvIII	Epidermal growth factor receptor variant III
EOT	End of treatment, defined as the last assessment for the protocol specified treatment phase of the study for an individual subject
EOI	End of infusion
EudraCT	European clinical trials database
eSAE	Electronic serious adverse event (form)
FDA	Food and drug administration
FFPE	Formalin-fixed, paraffin-embedded
FIH	First in human
GBM	Glioblastoma
GCP	Good clinical practice
GGT	Gamma glutamyltransferase
GLP	Good laboratory practice
Heart rate	Number of cardiac cycles per unit of time
HepBsAg	Hepatitis B surface antigen
HepCAb	Hepatitis C virus antibody
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
hr	Hour
ICF	Informed consent form
ICH	International conference on harmonisation
ICMJE	International committee of medical journal editors
IDH	Isocitrate dehydrogenase
IEC	Independent ethics committee
IHC	Immunohistochemistry
IND	Investigational new drug

Abbreviation or Term	Definition/Explanation
INR	International normalized ratio
IP	Investigational product
IPIM	Investigational product instruction manual
IRB	Institutional review board
IUD	Intrauterine device
IVD	In vitro diagnostic
IVSS	Intravenous solution stabilizer
kg	Kilogram
KM	Kaplan-Meier method
L	Liter
LDH	Lactate dehydrogenase
LKM 1	Liver kidney microsomal antibody 1
1st LGBM	Glioblastoma in first line maintenance
LTFU	Long term follow-up
MABEL	Minimum anticipated biological effective level
mAB	Monoclonal antibody
MDRD	Modification of Diet in Renal Disease
mg	Milligram
MHC	Major histocompatibility complex
min	Minute
mL	Milliliter
mM	Millimolar
MPV	Mean platelet volume
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MW	Molecular Weight
NASH	Nonalcoholic fatty liver disease, including steatohepatitis
ng	Nanogram
nM	Nanomolar
OR	Objective response
ORR	Objective response rate
PBMCs	Peripheral blood mononuclear cells
PK	Pharmacokinetic
PCR	Polymerase chain reaction
PD	Progressive disease
PD	Pharmacodynamic

Abbreviation or Term	Definition/Explanation
POR	Proof of receipts
pg	Picogram
Primary Completion	Defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early
PR	Partial response
RANO	Response assessment in neuro-oncology
RBC	Red blood cell count
rGBM	Recurrent Glioblastoma
RDW	Red cell distribution width
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SCR	Screening
SD	Stable disease
SEC	Self-evident corrections
SFUP	Safety follow up visit: defined as the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
SoC	Standard of care
Source Data	Information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	Defined as the first day that protocol specified investigational product(s)/protocol-required therapies is/are administered to the subject
$t_{1/2}$	Terminal-phase elimination half-life
TBL	Total bilirubin
TMZ	Temozolomide
TNF	Tumor necrosis factor
TPI	Toxicity probability interval
TTP	Time to progression
T2/FLAIR	T2-weighted fluid-attenuated inversion recovery
ULN	Upper limit of normal

Abbreviation or Term	Definition/Explanation
V_{ss}	Apparent volume of distribution at steady state
WBC	White blood cell
WHO	World health organization
w/v	Weight/volume
µg	Microgram

Table of Contents

List of Tables

List of Figures

[redacted]

List of Appendices

1. OBJECTIVES

1.1 Primary

The primary objective of this study is to:

- Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion in monotherapy (Arm 1) and in combination with AMG 404 (Arm 2) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and in the maintenance treatment phase of newly diagnosed glioblastoma or malignant glioma (maintenance setting, Group 2)

1.2 Secondary

The secondary objectives of this study are to:

- Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion either in monotherapy or in combination with AMG 404
- Evaluate the pharmacokinetics (PK) of AMG 404 in serum when administered by short term infusion in combination with AMG 596
- Evaluate the clinical benefit of AMG 596 monotherapy or AMG 596 in combination with AMG 404 as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO) (Okada et al., 2015) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent and in the maintenance setting
- Evaluate progression free survival rate at 6 and 12 months after initiation of treatment for any Part, Arm and Group of the study

1.3 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Disease

Glioblastomas belong to the group of highly malignant brain tumors representing one of the most lethal human cancers. The age-adjusted incidence of glioblastoma ranges from 0.59 to 3.69 per 100,000 persons worldwide (Ostrom et al., 2014). Despite aggressive surgical, radiologic and chemotherapeutic intervention, tumors progress

within months or even weeks leading to an overall survival of 12 to 15 months with almost no change in prognosis since the FDA's approval of temozolomide (TMZ) in 2005 (Omuro & DeAngelis, 2013).

The urgent medical need has driven the development of new immunotherapy concepts despite the classic dogma that the central nervous system is immune-privileged and hence inaccessible to potent antitumor immunity. The intriguing success of novel immunotherapeutic concepts in advanced melanoma, in non-small cell lung cancer and renal cell cancer in particular, together with new insights in relevant tumor antigens and expression of markers of immune regulation such as PD-L1 have provided grounds for clinical development of immuno-oncology agents targeting the central nervous system (Platten et al., 2016). Moreover, trafficking of functionally-active T-cells to the central nervous system (CNS) has been demonstrated (Gedeon et al., 2013). The regression of all intracranial and spinal glioblastoma lesions after multiple intracranial infusions of interleukin 13 receptor alpha 2 targeting CAR T-cell therapy was reported recently (Brown et al., 2016). Although this is only a single subject case report, the intriguing response provides preliminary evidence for safety and antitumor activity of T -cell--mediated immunotherapy in subjects with glioblastoma.

Epidermal growth factor receptor variant EGFRvIII

Epidermal growth factor receptor (EGFR) expression and enhanced EGF pathway signaling activity accompanied by amplification of the gene encoding EGFR have been documented in glioblastoma (GBM) (Mendelsohn & Baselga, 2006); (Mellinghoff et al., 2005), almost exclusively in isocitrate dehydrogenase (IDH) wildtype glioblastoma (Louis et al., 2016). About 50% of glioblastomas are positive for EGFR amplification, half of which express the accompanying EGFR mutation, encoding a truncated and constitutively active receptor termed EGFRvIII. Like native EGFR, mutant EGFRvIII is a membrane-bound receptor; however, the deletion results in a protein lacking 267 amino acid residues encompassing the extracellular ligand binding domain and characterized by a novel glycine residue occurring at the splice junction (Wong et al., 1992). While lacking an extracellular ligand binding domain, EGFRvIII has shown ligand-independent constitutive tyrosine kinase activity that stimulates downstream signaling pathways, which promote malignant growth (Mellinghoff et al., 2005). According to one meta-analysis (Chen, Xu, Yao, & Qin, 2015), there is currently insufficient evidence that either EGFR amplification or the EGFRvIII mutation has prognostic value in patients with glioblastoma. EGFRvIII is nevertheless considered a bona-fide tumor-specific antigen

found exclusively on tumor cells thereby making it an attractive antitumor treatment strategy. Targeting by a bispecific T-cell engager (BiTE®) has revealed promising antitumor activity in preclinical settings (Choi et al., 2013; Kischel et al., 2016).

AMG 596 is a BiTE® targeting EGFRvIII receptor as a tumor-specific antigen and T-cell receptor-associated complex cluster of differentiation 3 (CD3) on T-cells. AMG 596 demonstrates bispecific binding to EGFRvIII on tumor cells and CD3 on T cells, leading to formation of an immunological synapse and potent T-cell-induced cytotoxicity. AMG 596 showed high cytotoxicity activity against EGFRvIII expressing GBM cell lines in vitro and significantly prolonged survival of systemically treated mice versus control animals (Kischel et al., 2016). Furthermore, no direct AMG 596-related adverse changes were observed in a preclinical safety study in cynomolgus monkeys at doses of up to [redacted] mg/kg/day with a large exposure at serum concentrations of up to approximately 21 µg/mL.

Checkpoint inhibitors for treatment of Glioblastoma (GBM)

Immunotherapies with checkpoint inhibitors have been explored in GBM with limited success (Omuro et al., 2018) and response rates have been rarely above 10 percent (Wang et al., 2019). Reasons for failure are associated with (1) genetic patterns supporting immunosuppressive tumor microenvironment, eg PTEN mutations leading to cell clustering and lack to increase T cell infiltration, (2) evolutionary patterns promoting negative selection of immunogenic neoepitopes, and (3) greater increase in T cell diversity leading to failure of selective recruitment of lymphocytes to tumor (Zhao et al., 2019).

Nivolumab, a fully human IgG4 subtype programmed death-1 (PD-1) immune checkpoint inhibitor was evaluated in a large randomized clinical trial (Reardon et al., 2017) in monotherapy or combination with ipilimumab and monotherapy was compared versus bevacizumab in 369 patients with first recurrence of GBM in the phase 3 part (NCT02017717). At baseline, most patients in the nivolumab (nivo, 83%) and bevacizumab (bev, 84%) arms had measurable disease, and 40% (nivo) and 43% (bev) of patients required corticosteroids, receiving up to ≥ 4 mg/day. The 12-month OS was 42% in both monotherapy arms and median OS for nivolumab was 9.8 months compared to 10 months for bevacizumab. ORRs were 8% (nivo) and 23% (bev); median duration of response was 11.1 months (nivo) and 5.3 months (bev). Most common treatment-related AEs (≥ 10% of patients in either arm; nivo vs bev) were fatigue (21% vs 14%) and hypertension (1% vs 22%). Serious AEs (all causalities) were reported in

46% (nivo) and 35% (bev) of patients. Seizure (8% vs 6%) and malignant neoplasm progression (11% vs 7%) were the only serious AEs reported in ≥ 5% of patients in either arm.

Pembrolizumab, a humanized IgG4 anti PD-1 monoclonal antibody (mAb), was explored in GBM in a basket trial (Keynote-028) with the GBM basket of patients with any recurrence including two-thirds being treated after their first recurrence (Reardon et al., 2016). One partial response (ORR 4%) was observed within 25 patients and 12 patients (48%) presented with SD. Treatment-related AEs occurred in 19 (73.1%) patients, most commonly fatigue and rash (n=6 each, 23.1%). Four (15.4%) patients experienced grade 3–4 treatment-related AEs (lymphopenia, type 2 diabetes mellitus, arthritis, and syncope). Pembrolizumab in combination with bevacizumab was compared with pembrolizumab in 80 patients with recurrent GBM for the primary endpoint of 6-month PFS per RANO (NCT02337491). At a median follow-up of 25 months the 6-month PFS was 6.7% for pembrolizumab monotherapy and 25.3% for the combination (Reardon et al., 2018). Most commonly observed treatment-related AEs were headache (30%) and fatigue (17%) for pembrolizumab monotherapy.

Although PD-L1 expression has been reported in GBM specimen, the observed clinical results were discouraging (Berghoff et al., 2015). Emerging evidence of relevant immune cell activation through blockade of PD-1/PD-L1 axis comes from most recently published studies with neoadjuvant checkpoint blockade. Patients with recurrent GBM receiving neoadjuvant pembrolizumab prior to surgical debulking experienced significantly longer overall survival versus those receiving adjuvant, postsurgical pembrolizumab. In the neoadjuvant group, focal induction of PD-L1 in the tumor microenvironment and activation of tumor infiltrating lymphocytes, linked with upregulation of interferon gamma related genes suggesting relevant immune cell activation, were observed. Moreover, expanded T cell receptor clones correlating between tumor and blood with high overlap, and a decreasing monocytic population in the peripheral blood were associated with neoadjuvant pembrolizumab but not seen with adjuvant treatment only. Interestingly, dexamethasone was not found to impact upregulation of interferon gamma and T cell activation genes. Hence, only patients with baseline 4 mg/day or less dexamethasone were allowed to enroll. The authors concluded that an immune response leading to prolonged survival was induced by repeated PD-1 blockade whereby maintaining functionality of tumor-specific T cell clones, and by down-regulation of cell cycle related gene expression within tumor cells through T cell-mediated interferon gamma

response(Cloughesy et al., 2019). A similar approach with neoadjuvant administration of nivolumab to patients undergoing surgery for GBM indicates the onset of antitumor-directed immune pharmacodynamic effects after treatment with neoadjuvant nivolumab (Schalper et al., 2019).

Ultimately, to overcome hurdles for success of immunotherapies in GBM such as a limited number of infiltrated T cells and an upregulated immunosuppressive signature, the combination of checkpoint blockade with BiTE® treatment may be an alternative approach to achieve clinically meaningful tumor regression. The combination of checkpoint inhibitors with various BiTE® molecules in preclinical studies showed that cytotoxic potential, T cell activation and proliferation are strongly enhanced upon blockade of the PD-1/PD-L1 axis (Kufer et al., 2016, Osada et al., 2015). The addition of AMG 404, an anti-PD-1 mAb that is being developed by Amgen, to AMG 596 may support maintaining T cell activation by blocking PD-1 upregulation on T cells and avoid T cell exhaustion facilitated by the immunosuppressive microenvironment. The current study with AMG 404 will enable a deeper understanding of synergistic efficacy, toxicity, and pharmacodynamic profiles of the combination of AMG 404 and AMG 596.

2.2 Amgen Investigational Product Background AMG 596

2.2.1 Nonclinical Pharmacology

Nonclinical studies were performed in vitro and in vivo to investigate the mechanism of action of AMG 596 in redirecting human and cynomolgus monkey T-cells to lyse EGFRvIII-positive cells. No binding was observed in cell lines expressing other EGFR family members ((EGFR (HER1), HER2, HER3, and HER4)). In vitro cytotoxicity experiments demonstrated that AMG 596 selectively mediated redirected lysis of EGFRvIII-positive cells in the presence of human effector cells in a time- and dose-dependent manner, with mean half-maximal tumor cell lysis concentrations (EC_{50}) ranging from 0.137– 0.615 ng/mL. In addition, AMG 596-mediated cell lysis was also observed at varying ratios of effector-to-target (E:T) cell ratios.

In the presence of EGFRvIII-positive cells, AMG 596 induced a polyclonal activation of T-cells, resulting in the up-regulation of the T-cell activation markers CD25 and CD69, as well as the release of inflammatory cytokines ((interferon-γ, interleukin (IL)-2, IL-4, IL-10, and tumor necrosis factor (TNF)).

Mouse xenograft models of the human glioblastoma tumor cell line U-87 MG engineered to express human EGFRvIII were used in the nonclinical evaluation of the in vivo efficacy of AMG 596. NOD/SCID mice bearing subcutaneous or orthotopically injected

U-87 MG/EGFRvIII tumors were treated with AMG 596 or vehicle by daily intravenous bolus injections. AMG 596 monotherapy significantly inhibited subcutaneous tumor growth as well as prolonged survival in the orthotopic U-87 MG/EGFRvIII glioblastoma xenograft model. In addition, no macroscopic brain tumors were found in surviving animals at necropsy after treatment with AMG 596.

2.2.2 Nonclinical Pharmacokinetics

The toxicokinetics of AMG 596 have been previously analyzed in two studies in cynomolgus monkeys, after cIV infusions of [redacted] days. After a [redacted] day cIV infusion, AMG 596 C_{max} and AUC_{last} values were dose proportional between doses of [redacted] mg/kg/day, with mean C_{max} and AUC_{last} values ranging from 17–417 ng/mL and 2217-58245 ng*hr/mL, respectively. The highest AMG 596 exposures were observed after the [redacted] mg/kg/day dose. In the second study, AMG 596 was administered as a [redacted] day cIV [redacted] at doses of [redacted] mg/kg/day. The average steady-state concentrations (C_{SS}) at the [redacted] mg/kg/day dose levels were [redacted] µg/mL and [redacted] µg/mL, respectively. Serum concentrations of AMG 596 at the [redacted] mg/kg/day dose group were approximately 10-fold higher than the [redacted] mg/kg/day group, describing an approximately dose linear behavior after the first two weeks of treatment; [redacted] after the second week was attributed to the impact of AMG 596 exposures during the third and fourth week of treatment.

2.2.3 Toxicology

The potential toxicity of AMG 596 was evaluated in a Good Laboratory Practice (GLP) compliant [redacted] cynomolgus monkey toxicology study. AMG 596 was administered daily by cIV infusion at [redacted] mg/kg/day. Two [redacted] mg/kg/day males were euthanized on days 18 and 27 due to: a deterioration in clinical condition likely due to: complications at the catheter site and subsequent infection; skin ulcerations secondary to irritation from the dose administration jacket. [redacted]

[redacted]. Findings considered directly related to AMG 596 were mostly confined to clinical and anatomical pathology assessments and tended to be of low severity and/or showed no clear dose relationship. Changes in hematology parameters

were noted at either dose level tested including: decreased red blood cell (RBC) mass with increased reticulocytes and red cell distribution width (RDW), mildly to moderately decreased lymphocytes and basophils with associated decreased white blood cells, and mildly to moderately increased mean platelet volume (MPV). Among coagulation and clinical chemistry parameters, AMG 596-related changes at either dose level included: increased C-reactive protein (CRP), globulins and fibrinogen correlating with decreased albumin; increased cholesterol and triglycerides; decreased gamma glutamyltransferase (GGT); increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). A transient and minimal increase in MCP-1 was observed at the [redacted] mg/kg/day dose following start of infusion, while a minimal increase in IL-6 and MCP-1 was observed on day 18 for the male from this group euthanized on this day. Flow cytometry revealed transient decreases in T and NK cells on day 1. Females treated with [redacted] µg/kg/day also showed mildly increased bone marrow cellularity. [redacted] None of the other AMG 596-related changes were deemed adverse due to the magnitude of change and/or severity grading. The Highest Non-Severely Toxic Dose (HNSTD) was considered to be [redacted] mg/kg/day.

2.3 Amgen Investigational Product Background AMG 404

2.3.1 Nonclinical Pharmacology

AMG 404 is an IgG1 antibody; however, the Fc region has been modified to eliminate undesired interactions with Fc gamma receptors. The ligand blocking activity of AMG 404 was evaluated in three different assays using three different readouts and both cell-expressed, as well as recombinant, soluble ligands. In each assay, AMG 404 demonstrated the expected dose-dependent activity, indicating it is a potent inhibitor of human and cynomolgus monkey PD-1 binding.

2.3.2 Nonclinical Pharmacokinetics

The toxicokinetics (TK) of AMG 404 were characterized in a Good Laboratory Practice (GLP) study after weekly IV administration of [redacted] mg/kg or SC administration of [redacted] mg/kg for four consecutive weeks. Following repeat dose administration, AMG 404 exposure increased approximately dose-proportionally from [redacted] mg/kg as measured by C_{max} and AUC over 6 days. AMG 404 exposures were similar between male and female animals.

2.3.3 Toxicology

The potential for AMG 404 to cause acute release of cytokines from human peripheral blood leukocytes (PBL) in the presence of human endothelial cells (HUVECs) was evaluated in vitro. Under the conditions tested, AMG 404 did not induce cytokine release above background levels.

AMG 404 was evaluated in a [redacted] GLP toxicology study in cynomolgus monkeys. Doses of [redacted] mg/kg were administered by slow IV bolus, and doses of [redacted] mg/kg were administered SC (3 animals/sex/group). Animals were dosed once weekly (4 total doses). There were no AMG 404-related clinical signs or effects on body weight, food consumption, respiratory rate, body temperature, organ weights, or urinalysis parameters and no AMG 404-related ocular, electrocardiographic, neurologic, or macroscopic findings. AMG 404-related clinical pathology changes were limited to mild decreases in lymphocytes for females at all dose levels on Day 2 that were generally similar to control and/or baseline values on Day 9 and throughout the remainder of the study, and mildly increased C-reactive protein in some animals.

In conclusion, administration of AMG 404 by once weekly IV bolus or SC injection was well tolerated in cynomolgus monkeys at levels of [redacted] mg/kg IV and [redacted] mg/KG IV and SC.

Refer to AMG 404 Investigators Brochure for more information.

2.4 Risk Assessment

2.4.1 AMG 596 Monotherapy

At this time, there is limited clinical experience with AMG 596 in humans derived from first 15 subjects treated in this study and data are summarized in the AMG 596 Investigator's Brochure. Based on the AMG 596 BiTE® mode of action targeting EGFRvIII (expressed solely on cancer cells in glioblastoma), nonclinical data, and the clinical experience with other BiTE® molecules, the potential risks of AMG 596 include cytokine release syndrome (with associated signs and symptoms including fever, nausea, hypotension, tachycardia, asthenia, headache, rash, and dyspnea) and neurologic events.

The drug product for AMG 596 contains sucrose, and the estimated sucrose exposure following administration of AMG 596 in the two highest pre-planned dose escalation cohorts may exceed an estimated toxicology-based limit for parenteral administration of

sucrose. Cases of renal dysfunction have been reported with intravenous administration of some marketed products containing sucrose.

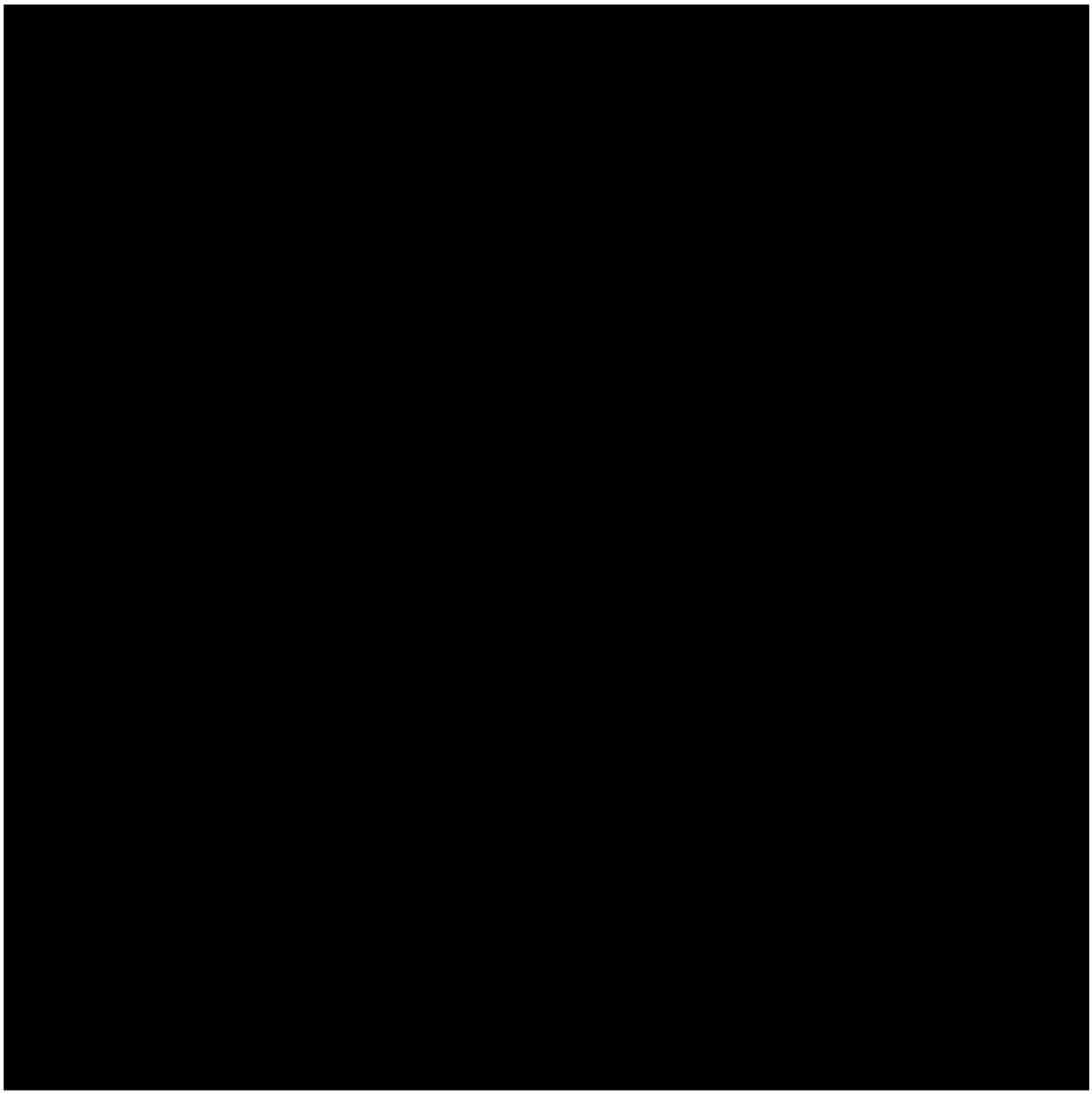
An antibody-drug-conjugate (AMG 595) targeting EGFRvIII was explored in a first in human (FIH) study (NCT01475006). Of the 31 subjects in the dose escalation analysis set of this study (all DLT-evaluable subjects), 10 subjects had DLTs (thrombocytopenia, grade 4 severity, and considered by the investigator as related to investigational product). The most common treatment-related adverse events occurring in 10% subjects overall were thrombocytopenia, fatigue, ALT increased, nausea, AST increased, and hypophosphatemia. However, toxicity in this study is obviously mainly caused by the toxic payload and therefore, the information may only be of limited importance for the risk evaluation of AMG 596.

For a listing of potential risks, see Table 1 below. Please also refer to the AMG 596 Investigator's Brochure for further description of potential risks.

Table 1. Potential Risks of AMG 596

Potential Risk	Description
Cytokine release syndrome (CRS)	Non-antigen-specific toxicity occurring as a result of high-level immune activation (Please see Lee et al., 2014) Signs and symptoms many include the following: • Constitutional – fever, rigors, fatigue, malaise • Neurologic – headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure • Respiratory – dyspnea, tachypnea, hypoxemia • Cardiovascular – tachycardia, hypotension • Gastrointestinal – nausea, vomiting, transaminitis, hyperbilirubinemia • Hematology – bleeding, hypofibrinogenemia, elevated D-dimer • Skin – rash Infusion reactions may be clinically indistinguishable from manifestations of CRS
Neurologic events	Patients with glioblastoma may present with generalized and focal neurologic signs and symptoms. A wide range of commonly observed neurological symptoms have been associated with the use of another BiTE® molecule, blinatumomab (anti-CD19 BiTE® antibody construct indicated for treatment of relapsed/refractory acute lymphoblastic leukemia). However, the spectrum of neurologic events has not been observed in clinical trials for other BiTE® molecules, and the neurotoxicity may in part be associated with targeting CD19.
Sucrose toxicity (with high dose exposure)	Estimated sucrose exposure following administration of AMG 596 in the two highest pre-planned dose escalation cohorts may exceed an estimated toxicology-based limit for parenteral administration of sucrose. Cases of renal dysfunction have been reported with intravenous administration of some marketed products containing sucrose.

[redacted]



2.5 Study Rationale

2.5.1 Rationale for AMG 596 Monotherapy

Glioblastomas are still known to represent a therapeutic challenge characterized by inevitable disease recurrence. The high medical need in this indication has driven the development of new immunotherapeutic approaches over the last several years. T-cell redirection to EGFRvIII-expressing tumor cells deserves attention as EGFRvIII is a unique surface receptor not expressed in normal brain tissue or outside the brain and is the most common EGFR mutation subtype in the brain. Preclinical studies have demonstrated that AMG 596, an EGFRvIII targeting BiTE®, facilitates interaction between T-cells and EGFRvIII-positive GBM cells independent of peptide-MHC expression or a functional T-cell receptor (Kischel et al., 2016). Furthermore,

inflammatory responses are able to occur in the brain, indicating leucocyte infiltration into the brain; additionally, penetration of the blood brain barrier by activated T-cells has been demonstrated. These observations together with the most recently published case report on response of glioblastoma to CAR T-cell therapy (Brown et al., 2016) support the opportunity for antitumor immune responses to AMG 596.

Upon recurrence after primary surgery, management of glioblastoma depends on age, performance status, histology, initial therapy response, time from original diagnosis and whether the occurrence is local or diffuse. In the case of diffuse or multiple tumor recurrences, palliative care is the preferred choice. In patients with localized disease, combination of surgery, nitrosourea-based therapies and radiation (standard re-irradiation or highly conformal) is used with poor results. A response to chemotherapy is unlikely after 2 consecutive agents have failed to produce a response (Stewart, 2002).

Moreover, no survival benefit has since been demonstrated for any new agent in a randomized trial (Mehta et al., 2017). With the current study, a new immunotherapeutic option will be explored. After the observation of a first objective response (partial or complete) in the recurrent setting, the safety and tolerability of AMG 596 will be further explored as a maintenance therapy following SoC for newly diagnosed disease according to local guidelines assuming that subjects with lower disease burden may better tolerate treatment at higher doses.

2.5.2 Rationale for the Combination of AMG 596 With AMG 404

BiTE treatment helps T cells to infiltrate tumor and become activated independent of the immunosuppressive microenvironment. However, preclinical evaluations showed that BiTE induced T cell activation is associated with upregulation of PD-1 on T cells, a known immune-regulatory mechanism that may lead to diminished T cell cytolytic activity resulting in impaired ability of T cells to eradicate the tumor. Anti-PD-1 therapy is intend to reverse this T cell exhaustion. Indeed, in vitro combination of AMG 596 with AMG 404 demonstrated more cytotoxic activity than AMG 596 alone.

We hypothesize that the addition of an anti-PD-1 antibody, such as AMG 404, may help maintain AMG 596-induced tumor cell killing by T cells resulting in improved antitumor activity in the clinical setting.

Initial signs of clinically meaningful antitumor effect with AMG 596 monotherapy in subjects with recurrent glioblastoma have been observed. In addition, monotherapy

administration of both novel products, AMG 596 and AMG 404, has been well tolerated, to date. Moreover, tolerability of anti-PD-1 antibodies has been demonstrated in subjects with glioblastoma in various clinical trials (Reardon et al., 2017, Schalper et al., 2019, Kufer et al., 2016, Osada et al., 2015). Considering the devastating nature of glioblastoma, the addition of AMG 404 to AMG 596, even in this early stage of the development of both investigational products, can be justified and can contribute to enrichment of treatment opportunities.

2.5.3 Dose Rationale

2.5.3.1 AMG 596 Monotherapy

The predicted human PK parameters of AMG 596 were derived from previous clinical experiences with AMG 211, a BiTE® molecule for solid tumor indications that targets CD3 located on T-cells and carcinoembryonic antigen (CEA) located on cancer cells of solid tumors (de Vries et al., 2015). Given the similarities in protein structure, molecular weight, and solid tumor targets, the PK of AMG 596 was expected to be similar to AMG 211 (AMG 211 Investigator's Brochure). In addition, previous clinical experience with other BiTE® antibody molecules, including blinatumomab and AMG 110, have exemplified the consistency of pharmacokinetics across the BiTE® platform, with renal excretion expected to be the primary route of elimination (based on MW) and observed terminal half-lives ranging between 2.1-4.4 hours. For these reasons, the PK of AMG 596 is expected to be consistent with previous BiTE® antibody molecules clinically, with a predicted half-life of 2.9 hours. Clinical PK data for AMG 596 can be found in the AMG 596 Investigator's Brochure.

The starting dose of AMG 596 was guided by the MABEL, an approach which has been safely used for previous BiTE® antibody molecules entering clinical testing. AMG 596-mediated redirected lysis of EGFRvIII-transduced U-251 MG glioblastoma cells (U-251 MG/EGFRvIII) was identified as a sensitive parameter for AMG 596 MABEL determination. AMG 596-mediated redirected lysis by T cells from 20 different donors was analyzed and based on individual dose-response curves a mean (± SEM) EC_{20} value of 0.07 ng/mL (± 0.004 ng/mL) was calculated and defined as in vitro MABEL of AMG 596. Using the assumptions of predicted human pharmacokinetics (PK) of AMG 596, a starting dose of [redacted] µg/day is predicted to achieve a serum C_{SS} of 0.088 ng/mL, which approximates EC_{20} concentrations of AMG 596-mediated cell lysis.

Additionally, the predicted CSF steady state concentrations of AMG 596 at this dose are 0.66 pg/mL and 3.2 pg/mL assuming 0.75% and 3.6% CSF penetration, respectively,

relative to serum exposures. These estimates were based on literature reported CSF exposures with other protein therapeutics, including monoclonal antibodies and blinatumomab, a CD19-targeting BiTE® (Burstein et al., 2013; Klinger et al., 2016). Furthermore, the lower molecular weight of AMG 596 (relative to monoclonal antibodies) and the impairment of the blood brain barrier in glioblastoma patients (eg, due to resection of tumors in the brain) may result in increased CSF and/or brain penetration (Tabrizi et al., 2010). The selected start dose and dose escalation will aid in reducing number of dose escalation steps necessary to reach CSF concentrations associated with BiTE® activity, along with the use of single-subject cohorts and approx. 3-fold escalations in dose in the earlier cohorts.

The starting dose is supported by the nonclinical toxicology studies in cynomolgus monkeys. AMG 596 cross-reacts with cynomolgus CD3 and has been well-tolerated at doses up to [redacted] mg/kg/day, with no AMG 596-related adverse findings detected at this dose level. At the starting dose of [redacted] µg/day, the safety margins based on the observed Css were 13 400-fold before potency adjustment and 1910-fold after correction for a 7-fold difference in AMG 596 potency between human and cynomolgus monkey effector cells. Although cynomolgus monkeys do not express EGFRvIII, any EGFRvIII- or CD3-mediated events that may require dose management, including the elevation of cytokines, can be resolved quickly due to the predicted short half-life of AMG 596 and the interruption of the cIV regimen, which will allow timely washout of AMG 596.

Dose escalation decisions will be guided primarily by safety and tolerability to AMG 596 and intermediate dose levels may be proposed if necessary. These high doses may be necessary to achieve adequate tumor exposure of AMG 596 due to the specificity of EGFRvIII expression in glioblastomas and the natural barriers associated with brain penetration of various therapeutics. It is also for this reason however, that systemic adverse events related to the BiTE® mechanism of action (eg, cytokine release syndrome) are expected to be limited. Prophylactic treatment with corticosteroids and/or the implementation of step-dosing regimens can be used to mitigate further risk of adverse events from BiTE® activity. A pharmacodynamic drug interaction study showed that AMG 596-induced cytokine release could be reduced by dexamethasone, but dexamethasone might result in a reduced cytotoxic potency of AMG 596 when co-administered to patients.

At higher doses of AMG 596, there is a risk of potential acute renal dysfunction due to the inclusion of 9% sucrose in the IV formulation, an excipient common to many

IV formulations. Although this risk is mainly associated with the [redacted] µg/day doses (which results in > 1.8 g/week of sucrose), sucrose-induced acute renal dysfunction is typically temporary and resolves within 7-15 days, and markers of renal function will be monitored throughout the study. In addition, sucrose exposures at the highest dose in the study are expected to be lower than those achieved with several marketed IV-administered therapies (eg, infliximab, immune globulin intravenous), in which sucrose exposures of up to 26 g/week were observed.

Dose escalation in Group 2 subjects can start at the highest AMG 596 monotherapy dose deemed to be tolerated by DLRT for Group 1 subjects.

2.5.3.2 AMG 596 in Combination With AMG 404

No clinical safety information is available for the combination of AMG 596 with AMG 404. Based on biological mechanism of action and initial clinical safety information for monotherapies with AMG 596 and AMG 404, adverse events caused by synergistic activation of T cells are expected.

The first-in-human dose exploration and expansion study evaluating AMG 404 in subjects with advanced solid tumors is currently ongoing. Preliminary PK results of AMG 404 in 11 subjects with advanced solid tumors after AMG 404 administration as short-term IV infusions (approximately 0.5 hours) [redacted] were available for dose levels of [redacted] mg (3 subjects, first and second dosing intervals) and [redacted] mg (8 subjects, first dosing interval). The nonclinical pharmacology findings and preliminary human PK results from the FIH study provide increased confidence towards achieving an efficacious dose with doses planned in the study and results were consistent with those for other therapeutic anti-PD-1 mAbs. Moreover, no dose-limiting toxicities (DLTs) were observed in any of the 12 subjects who have received AMG 404 doses up to [redacted] mg [redacted] Treatment-emergent adverse events were reported in 9 subjects (75.0%); the most frequently reported adverse events (≥ 3 subjects) were fatigue (4 subjects, 33.3%) and nausea (3 subjects, 25.0%). Three subjects (25.0%) had 5 adverse events that were grade 3 in severity (dehydration, edema, fatigue, urinary tract infection, and vomiting); no grade 3 adverse event preferred term was reported in > 1 subject.

Since AMG 404 doses up to [redacted] mg administered every 4 weeks have been shown to be tolerable, with the only treatment-related adverse event occurring in > 1 subject of nausea in 2 subjects (16.7%), the highest dose explored ([redacted] mg) will be used for combination therapy with AMG 596. If a higher AMG 404 dose will be declared as recommended phase 2 dose in the ongoing Phase 1 study (Study 20180143), such a

dose can be explored in additional cohort(s) in combination with AMG 596 whereby using the highest AMG 596 dose shown to be tolerated in the combination cohorts with AMG 404.

For AMG 596, the start dose in combination with AMG 404 treatment is based on the observation of pharmacodynamic effects observed at [redacted] µg/day in Group 1 subjects with recurrent malignant glioma. For Group 1 subjects, a dose of [redacted] µg/day administered in [redacted] infusion cycles will therefore be selected as first dose. The next AMG 596 pre-defined doses will be used for further dose escalation.

For Group 2 subjects, the starting dose of AMG 596 in combination with AMG 404 will be one dose level below the selected start dose for AMG 596 monotherapy (eg a start dose of [redacted] µg/day for AMG 596 monotherapy in Group 2 subjects leads to the selection of [redacted] µg/day as start dose for AMG 596 in combination with AMG 404 in Group 2 subjects). The next AMG 596 pre-defined doses will be used for further dose escalation.

To avoid cumulative toxicity associated with initial T cell activation after treatment start, a first dose of AMG 404 will not be given until [redacted] after start of the AMG 596 infusion. Prophylactic dexamethasone treatment as described in Section 6.5, should be given before starting any AMG 596 infusion. Dose escalation will start with single subject cohorts as a pharmacodynamic effect is expected resulting in a reduced cytotoxic potency of AMG 596 when co-administered with dexamethasone.

2.6 Clinical Hypotheses

- AMG 596 monotherapy and in combination with AMG 404 are safe and well tolerated in at least one dose level when administered in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent (Group 1) and in the maintenance setting (Group 2)
- AMG 596 monotherapy and/or in combination with AMG 404 can induce objective tumor shrinkage and/or overcome lack of response to standard of care (SoC) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in either recurrent or in the maintenance setting at a tolerable dose

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma exploring AMG 596 monotherapy (Arm 1) and combination of AMG 596 with AMG 404 (Arm 2). Each arm of the study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). This

study will enroll 2 groups of subjects according to disease stage, recurrent disease (Group 1) and maintenance treatment after SoC in newly diagnosed disease (Group 2).

Part 1: Dose Escalation

The purpose of dose escalation is to make a preliminary estimate of the RP2D /MTD of AMG 596 monotherapy and in combination with AMG 404. Treatment is divided into 2 periods: (1) DLT period 1 for [redacted] of AMG 596 infusion and (2) DLT period 2 for [redacted] of AMG 596 infusion (applies for both Arms). This distinction between DLT period 1 and DLT period 2 is maintained throughout dose escalation until the end of the dose escalation phase. Observations from other BiTE® studies have shown that the occurrence of initial non-cumulative toxicities associated with cytokine release within first 48 hours after start of infusion may limit dose escalation below doses assumed to be associated with anti-tumor activity. However, should the initial dose (DLT period 1) be limited by severe adverse events related to first dose effects (eg, cytokine release associated adverse events) an MTD for the first dose step may be defined. Further dose escalation in DLT period 2 is possible resulting in a step-dosing and a second (and higher) MTD. This approach supports the ongoing evaluation of initial toxicity, as well as toxicity after an MTD for the start dose has been defined.

The AMG 596 start dose based on preclinical evaluations for the estimation of the MABEL is [redacted] µg/day. Further pre-specified nominal AMG 596 doses for potential use in any dose escalation Arm are [redacted] µg/day. The dose level review team (DLRT) may consider treating at intermediate doses if required. If the MTD or a biological active dose considered the RP2D is not reached within the pre-planned nominal dose range, the DLRT may decide to expand the nominal dose range to dose levels [redacted] µg/day after careful consideration of all available safety, laboratory, and PK information. The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and separately in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2) and separately for AMG 596 monotherapy and in combination with AMG 404.

If the same AMG 596 doses are to be explored in monotherapy and in combination, the monotherapy cohort must be completed before enrollment in the combination cohort. In the multiple subject cohorts, a safety observation window of at least 72 hours must apply between start of subjects 1, 2 and 3 of each dose escalation cohort. Intra-subject dose escalation will be allowed to higher AMG 596 dose levels in subsequent treatment cycles

once a higher dose has been deemed safe by the DLRT. Subjects who do not proceed to a higher dose may continue at the original dose.

Group 1, Recurrent Disease

- *Dose Escalation in single subject cohorts*
  - AMG 596 monotherapy: In first cohorts AMG 596 will be administered as a cIV infusion for [redacted] at escalating doses with N=1 per cohort. In the single subject cohorts, only a limited number of subjects will be enrolled at dose levels anticipated to be lower than those at which visible pharmacodynamics activity including adverse events related to AMG 596 therapy will be expected. In addition, the investigator together with the subject will decide on subsequent treatment duration carefully. Subjects are allowed to stay on study in [redacted] cycles until discontinuation criteria apply.
  - Combination of AMG 596 with AMG 404: The starting dose of AMG 596 is [redacted]ug/day administered in [redacted]cycles and the defined AMG 404 dose is [redacted] mg every 4 weeks.
  - The cohort size will be increased to N=2-4 subjects (= Start of multiple subject cohorts) after observation of
    - Treatment-related adverse events of common terminology criteria for adverse events (CTCAE 4.0) grade 2 or higher and/or
    - Quantifiable cytokine levels in blood or CSF above baseline
- *Dose Escalation in multiple subject cohorts:*
  - Subjects in the first multiple subject cohort receive the same dose as the last single subject cohort.
  - All subjects receive AMG 596 in [redacted] infusion cycles until treatment discontinuation criteria apply.

  It is anticipated that dose-escalation will proceed according to the pre-planned nominal doses though intermediate dose levels may be used if required after reviewing all available safety data. When a first DLT is observed, the Bayesian logistic regression model (BLRM) will be used to guide dose level selection (Neuenschwander, Branson, & Gsponer, 2008). The cohort size will be N=2-4 subjects. On a limited basis, after agreement between the investigator and medical monitor, one additional subject may be allowed to be enrolled if the subject has been determined to be eligible and the cohort has been filled. In this case, all five subjects will be reviewed and assessed in the Dose Level Review Meeting (DLRM). After each cohort, the model's recommended MTD dose level for evaluation is the dose level with the highest probability of the target toxicity probability interval (TPI), but with a less than 0.25 probability of an excessive or unacceptable TPI. The target TPI is (0.20,

0.33], and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the DLRT after considering all information. Dose escalation will be completed when any of the following occurs:

- The maximum total sample size of N=45 DLT evaluable subjects (including single subject cohorts) is reached for AMG 596 monotherapy or N=30 DLT evaluable subjects for AMG 596 in combination with AMG 404.
- The BLRM model recommends the same dose level at least 2 times and that at least 6 subjects have been treated at the recommended RP2D/MTD dose level. If step-dosing required, this stopping criterion applies separately to each period.
- The highest planned dose level is reached without any DLTs being observed

Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease

- A first cohort will start after observation of a first objective antitumor response in Group 1 subjects with recurrent EGFRvIII-positive glioblastomas or malignant glioma. The starting dose of AMG 596 monotherapy in Group 2 will be decided by DLRT and will be the current highest dose deemed safe of Group 1. Treatment may consist either of [redacted] dose AMG 596 cIV [redacted] or step-dosing as established for recurrent disease. Further treatment cycles with [redacted] between cIV infusions will be provided until any of the treatment discontinuation criteria apply.
- The starting dose of AMG 596 in combination with AMG 404 for Group 2 will be one dose level below the selected start dose for AMG 596 monotherapy and an AMG 404 dose of [redacted] mg.
- The BLRM will be used to guide dose level selection. The cohort size will be N=2-4 subjects. The actual dose selected at each dose decision may be at or below the model's recommended dose as determined by the DLRT after considering all information.
- Dose escalation in Group 2 will be completed when any of the following occurs:
  - The maximum sample size of N=15 DLT evaluable subjects is reached for AMG 596 monotherapy or N=20 DLT evaluable subjects for the AMG 596 in combination with AMG 404.
  - At least 6 subjects have been treated at the recommended RP2D/MTD dose level
  - The highest pre-specified nominal dose level is reached without any DLTs being observed

Part 2: Dose Expansion

The purpose of dose expansion will be to further explore safety and to evaluate preliminary antitumor-activity in subjects with recurrent disease (Group 1) and in

subjects with maintenance setting (Group 2). It is anticipated that 15 subjects will be enrolled to Group 1 in Arm 1 and Arm 2, respectively. Up to 25 subjects will be enrolled to Group 2 in Arm 1 and Arm 2, respectively.

In Group 2 both for Arm 1 and Arm 2, the objective response rate (ORR) of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. For each arm, the ORR in Group 2 will be initially evaluated after 10 subjects are treated and have been evaluated at the first imaging scan or have dropped out before that. If ORR is lower than 5%, enrollment may be terminated due to futility. Otherwise, the ORR will be evaluated for additional new subjects and the futility stopping rules are calculated using a Bayesian predictive probability design (see Section 10.2 for details).

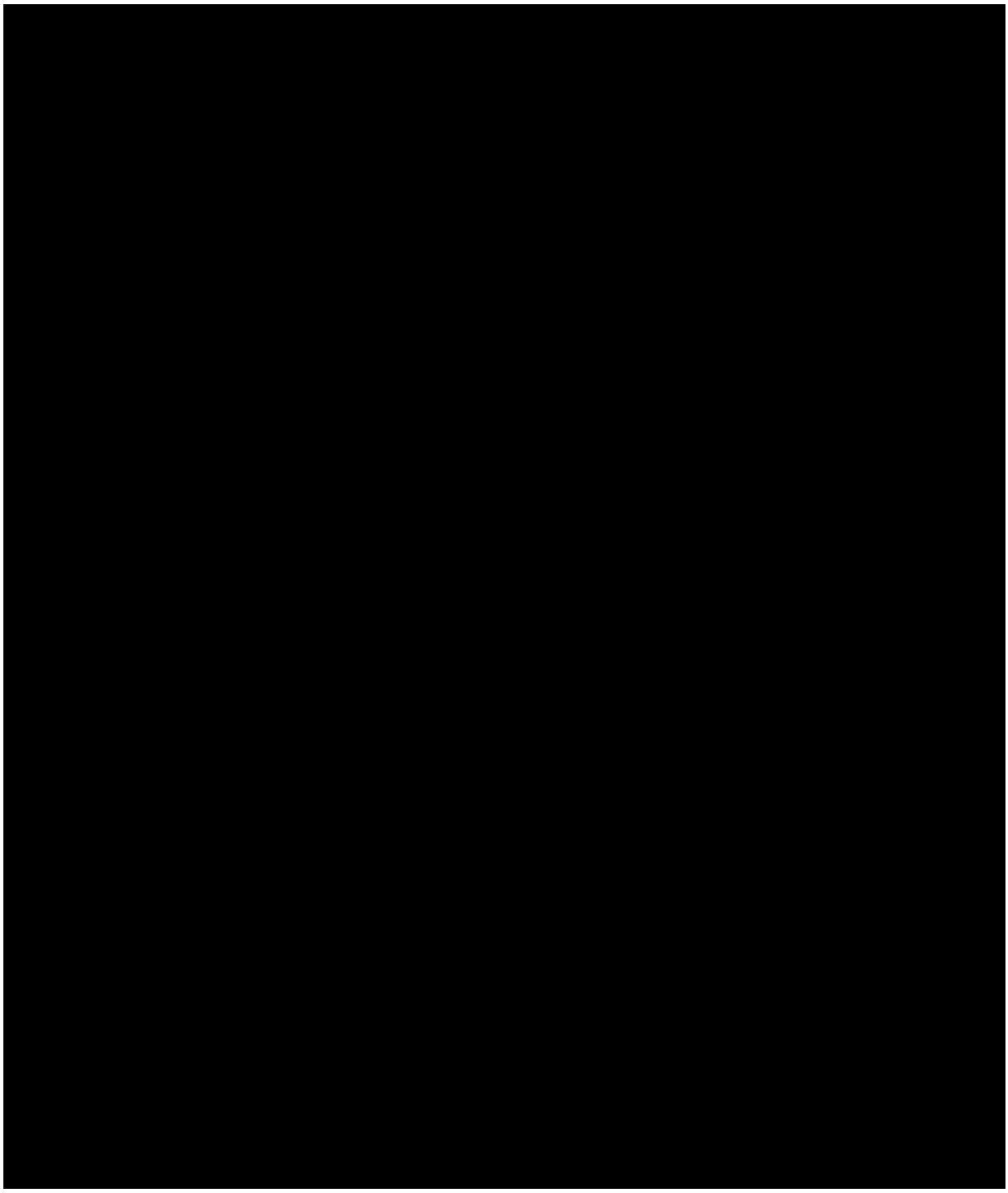
During dose expansion and separately for the monotherapy arm (combining data from Groups 1 and 2) and for the combination arm (combining data from Groups 1 and 2), Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. The threshold for holding enrollment is as follows.

Number of subjects	Hold enrollment if observing this many grade 4 or higher treatment-related adverse events
10	≥ 4
20	≥ 6
30	≥ 9
40	Study Complete

If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions: 1) Terminate the trial 2) Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication) 3) Continue dose expansion without any changes. See Section 10.2 for further details regarding the derivation of these thresholds.

A BLRM design may be used to update the estimate of the RP2D/MTD using data from subjects enrolled to dose escalation and dose expansion. Based on this revised RP2D/MTD estimate and reviewing all available safety data, the dose level for dose expansion may be revised.

The subjects enrolled in Part 2 dose expansion will be followed by imaging evaluation until the earliest of: clinically significant disease progression, death, consent withdrawal, start of new anti-tumor therapies or 12 months after treatment initiation. Subjects who stopped treatment will be contacted for long term follow up for up to 12 months after treatment initiation.



3.2 Number of Sites

This study will be conducted at approximately 12 or more sites in the United States, Australia and Europe. Additional countries or sites may be added if deemed necessary.

Sites that do not enroll subjects into an open cohort within 6 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”.

It is anticipated that around 190 subjects will be enrolled in the study.

It is anticipated that up to 100 subjects will be enrolled to Arm 1 in this study and up to 90 subjects will be enrolled to Arm 2 in this study.

For Group 1 (recurrent disease), the following are the planned sample sizes.

- In dose escalation, up to 45 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 30 DLT-evaluable subjects to combination Arm 2
- In dose expansion, up to 15 subjects will be enrolled to monotherapy Arm 1 and up to 15 subjects to combination Arm 2.

For Group 2 (maintenance setting), the following are the planned sample sizes.

- In dose escalation, up to 15 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 20 DLT-evaluable subjects to combination Arm 2
- In dose expansion, up to 25 subjects will be enrolled to monotherapy Arm 1 and up to 25 subjects to combination Arm 2.

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

Replacement of Subjects

Ineligible subjects (ie, subjects who were exposed to investigational product (IP) but after starting AMG 596 treatment were found to be ineligible) may be replaced. During dose escalation, a subject that is not DLT-evaluable will be replaced with another subject to the same dose level. A DLT-evaluable subject is defined as:

- Subject in the [redacted] cycle receiving a complete first cycle with 100% of the planned doses of investigational product, or
- Subject in the [redacted] cycle receiving at least 90% of the planned doses of investigational products, or
- Subject that has experienced a DLT.

Subjects will not be replaced after end of the DLT period.

3.4 Estimated Study Duration

The duration of this study will be approximately 4.5 years, with about 42 months for enrollment (a maximum of 30 months for the dose escalation cohorts, and 12 months for the dose expansion cohort) and 12 months protocol treatment period.

3.4.1 Study Duration for Subjects

It is anticipated that an individual subject will participate in the study for approximately 8 months including an effective screening period lasting 14 days, a treatment period lasting approximately 4 to 6 months, and a safety follow up period lasting 30 days (+/- 7 days). Additionally, there is a long term follow up for up to 12 months from treatment initiation. The actual duration for individual subjects will vary depending upon tolerability of AMG 596, 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 596 until he or she experiences an unacceptable adverse event, clinically significant disease progression, or he or she wishes to withdraw consent.

The safety follow-up study visit (SFUP) should occur 30 days (+/- 7 days) after the last dose of AMG 596 or prior to the initiation of other therapy, whichever occurs first. End of study for an individual subject is defined as the date of the final long-term follow up study visit (LTFU) when assessments and procedures are performed.

3.4.2 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; a primary analysis will be performed for each group separately when target enrollment in Part 1 and Part 2 is complete and each subject either completes 6 months on study or withdraws from the study.

End of Study: 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

4.1 Inclusion Criteria

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

102. Male or female, of at least 18 years of age

103. Eastern Cooperative Oncology Group (ECOG, Appendix F) Performance Status of ≤ 1

104. Life expectancy of at least 3 months, in the opinion of the investigator.

105. Must have pathologically documented, and definitively diagnosed World Health Organization (WHO) grade 4, glioblastoma or lower grade malignant gliomas with EGFRvIII positive tumor

106. Must have recurrent disease confirmed by MRI (Group 1) or completed SoC therapy such as surgery with adjuvant radiochemotherapy with or without maintenance temozolomide according to local standards for newly diagnosed disease (Group 2)

107. Group 1 subjects must have ≥ 1 index lesion by modified RANO criteria (Appendix D), exemption: non-measurable disease is allowed for subjects with re-surgery (surgery for recurrent disease) before start of screening; Group 2 subjects must have radiographically measurable disease or non-measurable disease by modified RANO criteria or both at the time of enrollment are allowed:

    - Bidimensionally measurable, contrast-enhancing lesions with clearly defined margins by MRI with perpendicular diameters of at least 10 mm x 10 mm and noted in more than one imaging slice
    - Imaging must be performed within 14 days of enrollment. Subject can be on stable dose steroid medication (systemic corticosteroid doses of ≤ 2 mg of dexamethasone (or equivalent) per day after consultation with Sponsor) for at least 5 days immediately before and during imaging study

108. Confirmed EGFRvIII positivity from pre-screening or confirmation at time of study enrollment required if prior treatment included EGFRvIII – or amplified EGFR- targeted therapy (one test sufficient, please refer to Section 7.2.1)

109. Archived tumor tissue from initial diagnosis or subsequent relapse for submission to central review

110. Hematological 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

111. Renal function as follows: serum creatinine < 2.0 mg/dL and estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2 by MDRD and urine protein quantitative value of < 30 mg/dL in urinalysis or ≤ 1+ on dipstick

112. Hepatic function as follows:

- Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 3.0 x upper limit of normal (ULN)
- Bilirubin ≤ 1.5 x ULN (unless considered due to Gilbert's syndrome or hemolysis)

4.2 Exclusion Criteria

201. History or evidence of central nervous system bleeding as defined by stroke or intraocular bleed (including embolic stroke) not associated with any antitumor surgery within 6 months before enrollment

202. Evidence of acute intracranial / intratumoral hemorrhage, except for subjects with stable grade 1 hemorrhage or fresh biopsy

203. Known hypersensitivity to immunoglobulins or to any other component of the IP formulation

204. Prior malignancy (other than in situ cancer) unless treated with curative intent and without evidence of disease for > 2 years before screening

205. Active infection requiring intravenous antibiotics that was completed < 1 week of study enrollment (day 1) with the exemption of prophylactic antibiotics for long line insertion or biopsy

206. Known positive test for human immunodeficiency virus (HIV)

207. Active hepatitis B and C based on the following results:

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

208. Unresolved toxicities from prior antitumor therapy, defined as not having resolved to CTCAE, version 4.0 grade 1 (with the exception of myelosuppression, eg, neutropenia, anemia, thrombocytopenia), or to levels dictated in the eligibility criteria with the exception of alopecia or toxicities from prior antitumor therapy that are considered irreversible (defined as having been present and stable for > 2 months) which may be allowed if they are not otherwise described in the exclusion criteria AND there is agreement to allow by both the investigator and sponsor

209. Antitumor therapy (chemotherapy, antibody therapy, molecular-targeted therapy, or investigational agent) within 14 days (Group 2 subjects) or 5 half-lives (whichever is longer: for Group 1 subjects) of day 1. Avastin, Pembrolizumab must be stopped 14 days prior to day 1

210. Treatment with non-topical systemic corticosteroids within 14 days before enrollment (day 1) (exemption:prophylactic treatment with dexamethasone as defined in section 6.5, and systemic corticosteroid doses of ≤ 2 mg of dexamethasone (or equivalent) per day after consultation with Sponsor,)

211. Prior participation in an investigational study (drug, procedure or device) within 21 days of study day 1

212. Major surgery within 7 days of study day 1 with the exception of biopsy and long line insertion

213. History or evidence of any other clinically significant disorder, condition or disease that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

214. Male and female of reproductive potential who are unwilling to practice highly effective method(s) of birth control while on study and through 30 days after receiving the last dose of AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404.

- Criteria for women of non-reproductive potential is as follows:
  - Postmenopausal as defined as:
    - Age of 55 years with cessation of menses for 12 months or more, OR
    - Age < 55 years and no spontaneous menses for at least 2 years, OR
    - Age < 55 years and spontaneous menses within the past year, but currently amenorrheic (eg, spontaneous or secondary to chemotherapy) AND with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone level > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) according to the definition of “postmenopausal range” for the laboratory involved; OR
  - History of hysterectomy; OR
  - History of bilateral oopherectomy

Highly effective methods of birth control include sexual abstinence (male, female); vasectomy; bilateral tubal ligation/occlusion; hormonal birth control or intrauterine device (IUD) (female).

215. Female who is lactating/breastfeeding or who plans to breastfeed while on study through 30 days after receiving the last dose of AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404.

216. Female with a positive pregnancy test.

217. Female planning to become pregnant while on study through 30 days after receiving the last dose of AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404 infusion.

218. Male who is unwilling to abstain from sperm donation while on study through 30 days after receiving the last dose of AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404.

219. Subjects 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.

The following Exclusion Criteria apply in addition for enrollment in combination cohorts with AMG 404

220. History of solid organ transplantation.

221. Prior treatment with anti-PD-1, anti-PD-L1, CTLA-4 or other checkpoint inhibitor drugs

222. Prior treatment with AMG 596 monotherapy arm is not eligible to enroll in the combination therapy arm.

223. Live vaccine therapies within 4 weeks prior to study drug administration

224. Evidence of interstitial lung disease or active, non-infectious pneumonitis

225. History of any immune-related colitis. Infectious colitis is allowed if evidence of adequate treatment and clinical recovery exists and at least 3 months interval observed since diagnosis of colitis.

226. Active or history of any autoimmune disease or immunodeficiencies. Subjects with Type I diabetes, vitiligo, psoriasis, hypo-or hyper-thyroid disease not requiring immune-suppressive treatment are permitted.

227. Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or cardiac arrhythmia requiring medication.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the informed consent form (ICF) for pre-screening (for subjects undergoing optional pre-screening) and for study participation before commencement of study-specific activities/procedures. The Investigator is to document the enrollment decision and date, in the subject's medical record and in/on the enrollment electronic case report form (eCRF). A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned for the study. Adverse events are to be collected for an eligible subject once they are enrolled in the study. Adverse events occurring during the screening

period will be documented as medical history unless the subject has been enrolled in the study.

Subjects diagnosed with malignant glioblastoma or malignant glioma are allowed to undergo pre-screening evaluations upon signing the pre-screening informed consent.

Subjects may alternatively enter directly into the screening period (defined as the point at which the subject signs the informed consent for study participation) without pre-screening.

Subjects will receive a unique subject identification number at the time of giving informed consent for either pre-screening or study participation (in case of not undergoing pre-screening). The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The unique subject identification number will consist of 11 digits. The first 3 digits will represent the last 3 digits of the protocol number (ie, 132). The next 5 digits will represent the country code and site number (eg, 26001) and will be identical for all subjects at a particular site. The next 3 digits will be assigned in sequential order as subjects are screened (eg, 001, 002, or 003). For example, the first subject to enter screening at site 26001 will receive the number 13226001001, and the second subject at the same site will receive the number 13226001002.

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 14 days before enrollment, unless otherwise indicated. Screening may pause between shipment of tissue samples for EGFRvIII analysis and availability of test result and this time will be deducted from screening time if no other evaluations were done in this screening pause. Laboratory assessments used to determine subject eligibility may be repeated once for confirmation (up to a total of 2 times during the 14-day screening period) if necessary before the subject is considered a screen failure. If any assessments are repeated during the screening period, the value that is closest to the enrollment date will apply for the determination of eligibility and should be recorded in the screening eCRF.

Subjects who do not meet the eligibility criteria within the 14-day effective 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 14-day screening period. Hepatitis serology and HIV test do not need to be repeated in case of re-screening if they were performed within 6 weeks prior to start of treatment with AMG 596. Test results confirming EGFRvIII-positivity expire with start of any antitumor therapy between re-screenings and need to be repeated in this case.

Subjects who are deemed ineligible 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. The Amgen representative will acknowledge receipt and send confirmation of cohort and dose level assignment for the subject.

Screening assessments of new subjects can start upon DLT period completion and before the dose level review meeting (DLRM) of the preceding dose. Sites are allowed to start pre-screening subjects after the study site activation.

5.1 Treatment Assignment

An Amgen representative will notify the site(s) in writing when a cohort is open to screen new subjects. This study will enroll 2 groups of subjects according to disease stage, recurrent disease (Group 1) and maintenance treatment after SoC in newly diagnosed disease (Group 2). Subjects will be treated either with AMG 596 monotherapy or with AMG 596 in combination with AMG 404 in the respective treatment arm according their individual eligibility and availability of treatment slots. If AMG 596 doses are different, mono- and combination therapy cohorts can run in parallel. If same AMG 596 doses will be explored in monotherapy and in combination, the monotherapy cohort must be completed before enrollment in the combination cohort.

Enrollment of Group 2 subjects can start after observation of a first objective response during Group 1 dose escalation.

At completion of the dose escalation cohorts, additional subjects (up to 15 Group 1 and up to 25 Group 2 subjects) will be enrolled in dose expansion cohorts to gain further clinical experience, safety and efficacy data in subjects with AMG 596 or AMG 596 in combination with AMG 404. The dose to be evaluated will be at or below the MTD estimated in the dose escalation cohorts.

The Sponsor will provide the exact treatment assignment (cohort) to sites including AMG 596 or AMG 596 and AMG 404 doses and schedule. The treatment assignment 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), Medical Device(s), and/or Combination Product(s)

The Amgen IPs used in this study include AMG 596, AMG 404 and intravenous solution stabilizer (IVSS).

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 596 and AMG 404.

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

6.2 Investigational Products

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 596 and IVSS

AMG 596 and the IVSS will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

AMG 596 is supplied as a sterile, single-use, preservative-free concentrate for solution for infusion in a vial containing 2 mg/mL AMG 596. The drug product is formulated with 10 mM sodium acetate, 9% sucrose, 0.01% (w/v) polysorbate 80, pH 5.5. The final container is a 5cc glass vial and contains 1 mL deliverable volume of AMG 596.

IVSS is supplied in 10 mL single-use glass vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate. It consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7.

The IVSS is intended to prevent adsorption of AMG 596 to surfaces of the infusion components.

6.2.1.1 Dosage, Administration, and Schedule for AMG 596

AMG 596 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines using preprogrammed infusion pumps approved for use in the country in which the subject is undergoing treatment. The drug will be administered as a cIV infusion at a constant flow rate for [redacted] cycles or over [redacted] cycles, until confirmed disease progression.

Subjects should be encouraged to remain well hydrated throughout the treatment period.

AMG 596 administration can cause dose dependent increase of peritumoral edema leading to development or worsening of depressed level of consciousness, a disease related event, which can be prevented by prophylactic administration of dexamethasone. Prophylactic use of corticosteroids is mandated for any subject receiving a new cycle of AMG 596 ([redacted]), with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) given within 1 hour prior to administration of AMG 596 and a second dose of dexamethasone given 8 mg IV 12 hours after start of the infusion. Subsequently, corticosteroids can be tapered at the discretion of the investigator based on clinical judgement. Same prophylactic use of dexamethasone is mandated for AMG 596 in combination with AMG 404 prior to the start of the AMG 596 infusion.

Prophylactic treatment with steroid (eg, dexamethasone) is also mandated before restarting of AMG 596 or otherwise clinically indicated (see Section 6.2.4.1 and Section 6.3.2).

Subjects will be hospitalized for the following periods:

Cycle 1:

- For the first [redacted] of AMG 596 monotherapy (Arm 1)
- For the first [redacted] of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on [redacted]
- For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2
- For additional 72 hours after AMG 596 step dose if necessary

Cycle 2 and all subsequent cycles:

- For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2
- For additional 72 hours after AMG 596 step dose if necessary.

Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator. 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.

The start dose for AMG 596 based on preclinical evaluations for the estimation of the MABEL is [redacted] µg per day. Further AMG 596 pre-planned dose levels are [redacted] µg per day; step-dosing can be introduced.

Intra-subject dose escalation for AMG 596 will be allowed to higher dose levels in subsequent treatment cycles once a higher dose has been deemed safe by the DLRT. Subjects who do not proceed to a higher dose may continue at the original dose. The MTD/RP2D or highest tested dose per group will be administered in the dose-expansion cohorts.

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. A new cycle for AMG 596 may begin +/- 2 days from the scheduled day 1 of the new cycle for logistical reasons.

AMG 596 should be administered through a central venous access. In the event that administration through a central venous access is not possible, AMG 596 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. Infusion bags should be changed in accordance with country regulations and local pharmacy standards for infusion of compounded sterile products up to 48 hours in the US and up to 96 hours in Australia and Europe. Specific details are provided in the IPIM.

Treatment breaks exceeding 21 days can be decided by the Investigator 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. If there is indication through the course of the study that subjects may derive additional or more rapid benefit by shortening the breaks between treatment cycles, the DLRM may decide to shorten the break periods between the first 4 treatment cycles.

The quantity administered, start date/time, stop date/time, and lot number of IP are to be recorded on each subject's eCRF.

6.2.1.2 Overdose

The effects of overdose of this product are not known. The daily AMG 596 dose may be up to 10% lower or higher in order to account for possible pump inaccuracies. A dose of up to 10% higher than the intended dose may not require specific intervention.

In case of overdose or medication error, the infusion should be immediately stopped. Consultation with the Amgen medical monitor is strongly recommended for prompt reporting of clinically apparent or laboratory adverse events possibly related to overdose. Consultation with the Amgen medical monitor is also strongly recommended even if there are no adverse events, in order to discuss the minimal duration of dose interruption. If the overdose results in clinically apparent or symptomatic adverse events, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event(s) should be recorded / reported as per Section 9.2. Resumption of AMG 596 is possible after consultation with the Amgen medical monitor and should adhere to the guidelines in Section 6.2.4.

A dose of > 10% higher than the intended AMG 596 dose will be considered clinically important and classified as a serious adverse event under the criterion of "other medically important serious event" per Section 9.2.2.2. The infusion must be restarted in the hospital.

6.2.1.3 AMG 596 Outpatient Dosing

If deemed stable by the investigator, a subject may continue AMG 596 cIV infusion as an outpatient. Vital signs should be within normal range or at baseline levels prior to the start of the infusion, per institutional guidelines, or deemed stable by the investigator. Subjects will receive a patient card indicating that the subject is participating in a clinical study. The patient card will also provide site contact details to be used in case of questions on the study or an emergency.

For infusion bag changes in the outpatient setting, the subject will either return to the study site or, in individual cases in alignment with site specific study contracts, be visited by a well-trained home health care service (HHCS) provider at the required frequency. If such contractually-agreed home visits for IV bag changes are required, the HHCS provider will 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 HHCS provider will be trained and will receive written instructions for storage of the IV bags. The home health care service provider will complete the study delegation log and will be authorized by the investigator before any study-related tasks are started. Refer to the home health care manual for detailed information on the storage, handling, and administration of AMG 596, mandatory procedures, and data collection requirements.

During cycle 1 and while the subject receives treatment in the outpatient setting, the study site personnel or HHCS provider will contact the subject on a daily basis to follow up on the status of the subject. The study site personnel or HHCS provider may also contact the subject via telephone to solve any issues related to the cIV infusion or infusion pump. All contacts will be monitored and documented, and the notes will be forwarded to the investigator and handled as source documents.

Any unexpected or unusual events identified during the home visits as well as any protocol deviations will be communicated promptly to the investigator. If any adverse event occurs in the outpatient setting, the subject will contact the site directly for further management.

The HHCS professionals provide 24-hour emergency on-call service for any pump related issues. In the event of an interruption of > 24 hours of the AMG 596 cIV infusion due to a pump related issue, restart of the infusion should be performed in the clinic/hospital under the supervision of the investigator or designee and the subject should be hospitalized for a minimum of 24 hours (see Section 6.2.4.1.). Infusion interruptions and restart times are to be recorded in the subject's medical records and in the eCRF.

6.2.2 Amgen Investigational Product AMG 404

AMG 404 is supplied in a 3 mL Type 1 glass tubing vial containing 1 mL deliverable volume of 70 mg/mL. The drug product is formulated with 10 mM acetate (sodium counterion), 9.0% (w/v) sucrose, 0.01% (w/v) polysorbate 80, pH 5.2 and will be prepared for IV administration by dilution.

6.2.2.1 Dosage, Administration, and Schedule for AMG 404

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

At the beginning of a treatment cycle a physician or nurse trained in emergency medical care must be available when the infusion of investigational product is started for immediate intervention in case of complications.

AMG 404 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.

AMG 404 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines.

The drug will be administered as an IV infusion at a constant flow rate over 30 minutes every [redacted] Subjects will be hospitalized for 24 hours after first administration of AMG 404 in Cycle 1 [redacted] of the AMG 596 infusion and should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each following AMG 404 infusion. Assessments should be performed as indicated in the Schedule of Activities.

The planned dose, start date, start time, stop date, stop time, dose administered, reason for dose change, and package lot number of AMG 404 are to be recorded on each subject's eCRF(s) and/or the site's study files.

6.2.2.2 Overdose

The effect of overdose of this product are not known.

6.2.3 Dose Escalation, Stopping Rules and Dose-limiting Toxicities (DLTs)

The preliminary estimate of MTD will use BLRM design. Refer to Section 10.2 for further details of stopping rules.

A DLT will be defined as any of the following occurring in a subject during the DLT period (first [redacted] treatment days for both AMG 596 monotherapy and in combination with AMG 404) and regarded to be related to AMG 596 and/or AMG 404. For adverse event severity grading see Section 9.2 (Adverse Events). The Common Terminology Criteria for Adverse Events (**CTCAE version 4.0**) will be used to assess toxicities/adverse events with the exception of cytokine-release syndrome (CRS) with grading performed according to the recommendations provided in Appendix E.

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 < 50 × 10^9/L > 7 days or clinically significant bleeding
- Lymphopenia of any grade is not considered a DLT

Non-hematological DLTs

- Any grade 4 non-hematological toxicity
  - Laboratory parameters of grade ≥ 3, not considered clinically relevant**,** and improved to grade ≤ 2 within 72 hours will not be considered DLT (for ALT and GGT elevations grade ≥ 3, not considered clinically relevant, and improved to grade ≤ 2 within 7 days due to the long half-life of these parameters)
- Any grade 3 or higher non-hematological toxicity if:
  - Nausea and vomiting, which is refractory to anti-emetics
  - Flare-up of pain because of potential increase in tumor volume is not regarded as a DLT
  - Grade 3 non-hematologic toxicity lasting > 3 days despite appropriate treatment
  - Grade 3 fatigue will not be classified as DLT, irrespective of duration
  - Grade 3 acute kidney injury
  - Any grade 3 seizure, ataxia or encephalopathy
  - Other grade 3 neurologic-related adverse events lasting > 3 days despite appropriate treatment
  - Neurologic-related adverse event leading to treatment interruption that needed more than 1 week to resolve to CTCAE grade ≤ 1
  - Any grade 3 endocrinopathy that cannot be adequately controlled by hormonal replacement

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.

The dosing schedule is described by a schema in the protocol synopsis.

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

6.2.4.1 AMG 596

Dose Delay or Dose Reduction

Any clinically relevant (as determined by the investigator) grade 4 adverse event related to IP that does not meet the DLT criteria should lead to a dose delay and/or a dose reduction. The decision if a dose delay or reduction will be performed is up to the investigator`s discretion. The sponsor may be consulted.

In addition, cytokine release syndrome of ≥ grade 3 (Appendix E) should lead to dosing interruption and treatment with immunosuppressive therapies should be performed (see Section 6.3 for details).

In case of re-appearance of the same grade 4 adverse event, IP should be permanently discontinued.

For persistent or re-occurring clinically relevant grade 3 adverse event related to IP, a dose delay or a dose reduction should be considered.

Infusion Interruption

Significant events requiring a change in treatment will be managed by immediate infusion interruption and should be documented in source documents and in the eCRF:

- The subject experiences a DLT as defined in Section 6.2.3.
- The subject experiences a clinically relevant grade 4 adverse event related to IP (see above)
- The subject meets criteria for discontinuation of IP as described in Section 8.3
- Technical problem with the infusion pump
- The investigational product is incorrectly prepared or administered (eg, overdose)

Restarting the Infusion

Treatment may resume if the interruption is ≤ 21 days:

- 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 or delays.
- The toxicity has resolved to ≤ grade 1. The infusion can be restarted according to guidelines presented in Table 3 and Table 4. Non-hematological Criteria for Dose Reduction.
- The toxicity occurred during the DLT period and 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 and should be performed in the clinic/hospital under the supervision of the investigator or designee and the subject should be hospitalized for a minimum of 24 hours when the infusion interruption meets the following criteria:

- associated to an AE, or
- interruption > 24 hours due to a pump related issue.

The restart 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 (eg, pump related

issue) or the interruption was > 24 hours independent of reason. Prophylactic treatment with steroid (eg, dexamethasone) is mandated before restarting of AMG 596. If step-dosing was already performed at the start of a cycle, the infusion should be restarted with step-dosing again if the infusion interruption was [redacted].

Subjects in [redacted] that have a treatment interruption during cycle 1 should be allowed to complete a total of [redacted] infusion, and subjects in [redacted] cycles that have a treatment interruption during cycle 1 should be given the opportunity to complete a total of [redacted] of infusion even though these may not be DLT evaluable subjects. Replacement of subjects in [redacted] off schedule cohorts that have a treatment interruption during cycle 1 will require discussion on a case by case basis between sponsor and investigator.

Restart after an interruption lasting [redacted] may be allowed after careful risk-benefit evaluation and requires discussion between investigator and sponsor. Hematological criteria for dose reduction are presented in Table 3 and non-hematological criteria are presented in Table 4. Dose reduction is possible with re-treatment at 1 dose level lower (Section 6.2.4.1)

Table 3. Hematological Criteria for Dose Reduction

CTCAE Grade	ANC (10^9/L)	Platelets (10^9/L)	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, consider re-escalation if completely recovered to baseline and no new toxicity occurred within 7 days of infusion.

Table 4. Non-hematological Criteria for Dose Reduction

CTCAE Grade*	Dose Delay	Dose Reduction	Comment
Non-hematological			
Cytokine release syndrome, tumor lysis syndrome, acute kidney injury			
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 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
* For CRS criteria defined in Appendix E apply

6.2.4.2 AMG 404

Dose Delay or Dose Reduction

Each subject will stay on the dose level assigned until treatment needs to be stopped. The reason for dose withholds and dose delays is to be recorded on each subject's CRF. Specific guidance for management of adverse events associated with AMG 404 are provided in Appendix G

Immune-related Adverse Reactions

Adverse events following the administration of AMG 404 may represent an immunologic etiology. Based on clinical experience with other anti-PD-L1 therapies, these immune-related toxicities may occur shortly after the first dose to several months after the last dose of treatment and may affect more than one body system simultaneously. Early recognition and management are critical to reduce complications.

Most immune-related adverse events require adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests, such as bronchoscopy, endoscopy, or skin biopsy, may be included as part of the evaluation.

Based on the type and severity of the immune-related adverse event, withholding or permanent discontinuation of AMG 404 may be required, in addition to treatment with corticosteroids and/or other therapies. Dose modification and toxicity management guidelines for immune-related adverse reactions are provided in Appendix G.

Infusion-related Reactions

Infusion-related reactions may occur with the administration of AMG 404. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain. If an infusion-related reaction is suspected, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform and ECG if the patient is experiencing chest pain or sustained tachycardia.

For mild or moderate infusion-related reactions, interrupt or slow the rate of infusion. For severe or life-threatening infusion-related reactions, permanently discontinue AMG 404. Treatment guidelines for infusion reactions associated with the administration of AMG 404 are provided in Appendix H.

6.2.5 Permanent Discontinuation

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

- Dose-limiting or other unmanageable toxicity. For exemption, please see Section 6.2.3).
- Clinically significant disease progression or deterioration.
- Occurrence of neurologic-related adverse event considered related to AMG 596 and/or AMG 404 by the investigator and meeting one or more of the following criteria:
  - Grade 3 seizure, ataxia or encephalopathy
  - A neurologic-related adverse event CTCAE grade 4
  - A neurologic-related adverse event leading to treatment interruption that needed more than 1 week to resolve to CTCAE grade ≤ 1
- Occurrence of acute kidney injury considered related to AMG 596 and/or AMG 404 by the investigator and meeting one or more of the following criteria:
  - Creatinine > 3x baseline or > 4.0 mg/dL and not recovered to CTCAE grade 1 or ≤ 0.3 mg/dL within 21 days
  - Hemodialysis required
- Subject's request
- Subject or investigator not compliant with the study protocol
- Occurrence or progression of a medical condition which, in the opinion of the investigator after medical consideration, is not associated with the disease under study and should preclude further participation of the subject in the study
- Pregnancy
- A DLT leads to permanent discontinuation unless the following criteria apply, in which case a restart of treatment at the same or a lower dose may be allowed:
  - The AE (including relevant lab values) is reversible and improves to grade ≤ 1 or baseline within 14 days
  - The patient is experiencing clinical benefit as assessed by the investigator
  - There is agreement between the investigator and the Amgen Medical Monitor that treatment may be restarted
  - The subject is willing to continue treatment after the investigator has led an appropriate discussion of potential risks and benefits with the subject

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 end of treatment (EOT) and safety

follow up (SFUP) 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 Specific Recommendations for Cytokine Release Syndrome, Neurologic Events and Hepatotoxicity

6.3.1 Cytokine Release Syndrome (CRS)

Cytokine release syndrome is clinically defined and may have various manifestations. Most cancer immunotherapies bear the risk of cytokine-associated toxicity, also known as cytokine release syndrome caused by non-antigen specific high level immune activation (Lee et al, 2014 and Appendix E). Signs and symptoms of CRS may include:

- Constitutional – fever, rigors, fatigue, malaise
- Neurologic – headache, mental status changes, dysphasia, tremors, dysmetria, gait abnormalities, seizure
- Respiratory – dyspnea, tachypnea, hypoxemia
- Cardiovascular – tachycardia, hypotension
- Gastrointestinal – nausea, vomiting, transaminitis, hyperbilirubinemia
- Hematology – bleeding, hypofibrinogenemia, elevated D-dimer
- Skin – rash

Subjects may be at an increased risk for cytokine release syndrome during the first few days following the initial infusion of AMG 596 and/or AMG 404. Cytokine release syndrome may be life-threatening or fatal. Infusion reactions may be clinically indistinguishable from manifestations of cytokine release syndrome. Throughout the infusion with AMG 596 and/or AMG 404, monitor subjects for clinical signs (eg, fever, tachycardia, dyspnea, tremors) and laboratory changes (eg, transaminase increase) which may be related to cytokine release syndrome. In the event of CRS, an unscheduled blood sample should be collected to measure cytokine levels.

Grading of cytokine release syndrome should be performed according to the recommendations provided by Lee et al, 2014. (see Section 13 and Appendix E).

Interventions for cytokine release syndrome will be determined by its particular manifestations and magnitude in each subject. Pyrexia may be managed with paracetamol/acetaminophen. Management of hypotension should be managed by volume resuscitation and, in the event that it is not sufficient or if there is evidence of volume overload, pressor support may be added, with the type of vasopressive agent determined by the investigator depending on the totality of observed hemodynamic parameters (heart rate, cardiac output, central venous pressure).

For grade 2 CRS, the study drug should be interrupted and monitoring and management of CRS symptoms should be performed as described above and according to published recommendations by Lee et al, 2014 (Appendix E). The study drug should be permanently discontinued for grade 2 CRS not improving to grade ≤ 1 within 7 days (Appendix E).

For grade 3 or greater cytokine release syndrome, the study drug should be interrupted and immunosuppressive therapies should be provided. Corticosteroids such as dexamethasone or methylprednisolone are the preferred choice for immunosuppression. Typical doses for dexamethasone are 8 mg IV q8 hours with subsequent tapering following symptom resolution. Tocilizumab has been reported to be efficacious in this setting at a dose of 4-8 mg/kg as a single dose. However, due to the reported potential aggravation of IL-6 levels in CNS in association with tocilizumab treatment decision should include careful risk-benefit evaluation. The study drug should be discontinued for grade 3 CRS not improving to grade ≤ 2 within 5 days or grade ≤ 1 within 7 days (Appendix E).

For grade 4 cytokine release syndrome, the study drug should be interrupted immediately and permanently discontinued. The subject should be transferred to an intensive care unit (Appendix E). After observation of first DLT (in DLT period 1) associated to cytokine release-associated adverse events, step dosing and/or prophylactic treatment with steroids (dexamethasone) is recommended to mitigate the cytokine release syndrome risk in further subjects.

Prophylactic dexamethasone treatment according to the following schema will be recommended to all subject after the observation of a first cytokine release syndrome of grade 2 (see Appendix E) or higher.

- Dexamethasone at a dose of 4 to 8 mg or equivalent corticosteroid will be administered orally or IV
  - 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 for first 24 hours of the infusion
- 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. Close monitoring of blood glucose levels is recommended in such a case. Further variations may be needed that should be discussed and agreed upon in a DLRM.

6.3.2 Infusion Interruption/Dose Modification due to Neurologic Events

Patients with glioblastoma or malignant glioma may present with generalized symptoms (eg, headaches, cognition and personality changes) and focal signs (eg, hemiparesis, sensory loss, visual field disturbances) (Omuro and DeAngelis, 2013).

Recommendations for management, including interventions and infusion interruptions for neurologic-related adverse events, are presented in Table 5. As neurologic events may be anticipated in the study population, guidance regarding reporting of safety events, including disease-related and adverse events, is provided in Section 9 (Safety Data Collection, Recording, and Reporting).

Table 5. Management of Neurologic Events (by Severity)

CTCAE Grade	Intervention	Instructions for Infusion Interruption or Permanent Discontinuation
3	Perform physical exam, assess vital signs and conduct safety laboratory tests Depending on the nature of the adverse event, additional measures (eg, CSF investigations, contrast-enhanced MRI of the head) can be taken upon discretion of the investigator MRI should also be considered for subjects who permanently discontinue treatment at the discretion of investigator	Immediately interrupt AMG 596 Restart AMG 596 infusion within 2 weeks, but not earlier than 72 hours (3 days) after the infusion has stopped, if the event resolves to grade ≤ 1 within 7 days Delay AMG 404 dosing until day 8 after AMG 596 restart if AMG 404 dosing was scheduled during interruption Permanently discontinue AMG 596 and AMG 404 if considered by the investigator related to study drug and if there is no improvement to grade ≤ 1 within 7 days
4	Perform physical exam, assess vital signs and conduct safety laboratory tests Depending on the nature of the adverse event, additional measures (eg, CSF investigations, contrast-enhanced MRI of the head) can be taken upon discretion of the investigator Conduct MRI for subjects who permanently discontinue treatment	Immediately interrupt AMG 596 Permanently discontinue AMG 596 and AMG 404

CSF – cerebrospinal fluid, CTCAE – Common Terminology Criteria for Adverse Events, MRI – magnetic resonance imaging

For subjects who experience serious neurologic adverse events leading to treatment interruption, if the event has decreased to at least CTCAE grade 1 within 1 week,

treatment may be restarted within 2 weeks, but not earlier than 72 hours (3 days) after the infusion was stopped.

Seizure

If the neurologic event was a seizure (CTCAE grade 2 or above), appropriate prophylactic anticonvulsant treatment (a therapeutic dose of eg, phenytoin or levetiracetam) can be administered during the next treatment cycle. In case of occurrence of seizure grade 3, the investigational products will have to be stopped immediately and treatment will be permanently discontinued, and investigations associated with and previously described for a CTCAE grade 3 or higher neurologic-related adverse events, must also be performed.

Depressed level of consciousness

Depressed level of consciousness is a common neurological sign of intracranial pressure increase. AMG 596 may cause inflammation at the site of the tumor, leading to worsening of increased intracranial pressure resulting in neurological toxicity including a depressed level of consciousness.

Prophylactic use of corticosteroids is mandated for any subject receiving a new cycle of AMG 596 ([redacted]), with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) given within 1 hour prior to administration of AMG 596 and the second dose of dexamethasone 8 mg IV given 12 hours after start of the infusion, and subsequent tapering at the discretion of the investigator. Prophylactic treatment with steroid (eg, dexamethasone) is also mandated before restarting of AMG 596 or otherwise clinically indicated (see Section 6.3).

6.3.3 Hepatotoxicity Stopping and Rechallenge Rules

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

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

Both investigational products 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.

6.3.5 Criteria for Conditional Withholding of Amgen Investigational Products due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen investigational products 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 products 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

For transaminitis of CTCAE grade 3 or 4 suspected to be caused by cytokine release infusion interruption and discontinuation criteria should apply as defined in Appendix E.

AMG 596 and AMG 404 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 (see Section 6.3.3 and Section 6.3.6.)

6.3.6 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 and investigator, after consultation with Sponsor.

If signs or symptoms recur with rechallenge, then the investigational products should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.2.5) should never be rechallenged.

6.4 Other Protocol-required Therapies

There are no other protocol-required therapies. All recommended 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 therapies. Please also refer to Section 6.4 for concomitant therapy.

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 6.8. Concomitant therapies are to be collected from informed consent through to the SFUP. Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected. 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 596 and AMG 404 treatment (see Section 6.3).

Recommendations for prophylactic anticonvulsant treatment for adverse events of seizure (CTCAE grade 2 or above) are provided in Section 6.3.2.

Prophylactic use of corticosteroids is mandated for any subject receiving a new cycle of AMG 596 ([redacted]), with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) given within 1 hour prior to administration of AMG 596 and the second dose of dexamethasone 8 mg IV given 12 hours after start of the infusion, and subsequent tapering at the discretion of the investigator. Same prophylactic use of dexamethasone is mandated for AMG 596 in combination with AMG 404 prior to the start of the AMG 596 infusion.

Prophylactic treatment with steroid (eg, dexamethasone) is also mandated before restarting of AMG 596 or otherwise clinically indicated (see Section 6.3.1 and Section 6.3.2).

6.6 Medical Devices

The investigational products 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 and as specified in Section 6.2.1 and Section 6.2.2. Investigational products, concentrates for solution for infusion, will be prepared in bags for IV infusion and AMG 596 will bedelivered through infusion lines with a 0.2 µm in-line filter. Both are compatible with the investigational product as described in the respective IPIM.

Additional details for the use of the IV bag and infusion lines and their specifications are provided in the respective IPIM. Those devices that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints

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

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

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

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

Any anti-tumor therapy other than the investigational products are not permitted, including cytotoxic and/or cytostatic drugs, hormonal therapy (unless treatment for endocrinopathy), immunotherapy or any biological response modifiers, any other investigational agent, other immunosuppressive therapies. Corticosteroids are

exceptions as described in Section 6.3 and Section 6.5 for management of CRS or neurologic adverse events.

Subjects who received AMG 596 as monotherapy are not allowed to participate in the combination therapy with AMG 404.

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 21 days of study day 1
- Major surgery within 7 days of study day 1, with the exception of biopsy and long line insertion
- Enrollment into another investigational drug or device study

7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 6. Schedule of Assessments-dose-escalation Cohort [redacted] Infusion Cycle 1

	Optional Pre-SCR	SCR	Treatment Period - Dose Escalation [redacted]																		
Cycle			1																		
Cycle Day	[redacted]																				
				Hours Relative to start of infusion																	
			Pre-dose	0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48		EOI	0.5	2	4	8	24
GENERAL AND SAFETY ASSESSMENTS																						
Informed consent	X	X																				
Hospitalization[a]			X																			
Medical History		X																				
Concomitant Medications		X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Serious adverse events		X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Adverse events [h]			X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Clinical Evaluation [b]		X	X											X	X	X	X					X
Neurological Evaluation		X	X												X		X					
Vital signs, pulse oximetry [c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X
ECG triplicate measurement		X	X												X		X					
LABORATORY ASSESSMENTS																						
Serum pregnancy test [d]		X	X																			
Coagulation		X	X											X	X	X	X					
Hematology, Chemistry		X	X											X	X	X	X					
Blood Glucose Test		X	X						X					X	X	X	X					
Cytokines / CRP (local lab)		X	X						X					X	X	X	X					X
Urinalysis/Dipstick		X	X												X		X					
Hepatitis Serology, HIV, HLA		X																				
[redacted]																						
INVESTIGATIONAL PRODUCT DOSING																						
AMG 596	[redacted]																					
BIOMARKER ASSESSMENTS																						
[redacted]																						
DISEASE ASSESSMENTS																						
Imaging [g]		X																				

Footnotes defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycle 1 will be for a minimum of 8 days.

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and following this every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[redacted]

[g] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[h] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

Table 7. Schedule of Assessments-dose-escalation Cohort [redacted] Infusion Cycle 2 and all Subsequent Cycles

	Treatment Period - Dose Escalation [redacted]																				
Cycle	2 and all subsequent cycles																				
Cycle Day	[redacted]																				
	Hours Relative to start of infusion																				Every 3 months (+/- 2 weeks)
	Pre-dose	**0.5**	**1**	**2**	**3**	**4 (+1)**	**6**	**8**	**12**	**16**	**20**	**24**	**48**		**EOI**	**0.5**	**2**	**4**	**24**			
GENERAL AND SAFETY ASSESSMENTS																						
Informed consent																						
Hospitalization[a]							X															
Concomitant Medications	X	→																				→
Serious adverse events	X	→																				→ X [h]
Adverse events	X	→																				→
Clinical Evaluation[b]	X											X	X	X	X				X	X	X	
Neurological Evaluation	X												X		X					X	X	
Vital signs, pulse oximetry[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	
ECG triplicate measurement	X												X		X					X	X	
LABORATORY ASSESSMENTS																						
Serum pregnancy test[d]	X																					
Coagulation	X											X	X	X	X					X	X	
Hematology, Chemistry	X											X	X	X	X					X	X	
Blood Glucose Test	X						X					X	X	X	X					X	X	
Cytokines / CRP (local lab)	X						X					X	X	X	X				X	X	X	
Urinalysis/Dipstick	X												X		X					X	X	
Hepatitis Serology, HIV																						
[redacted]																						
INVESTIGATIONAL PRODUCT DOSING																						
AMG 596	[redacted]																					
BIOMARKER ASSESSMENTS																						
[redacted]																						
DISEASE ASSESSMENTS																						
Imaging[e]																			X		X	X

Footnote defined on the next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycles 2 and subsequent cycles will be for a minimum of 72 hours until cycle 5 and 48 hours from cycle 6 onwards (per treating investigator's discretion).

[b] Clinical evaluations will include physical exam, ECOG, and weight.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and following this every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed every 10 to 12 weeks from start of treatment, and at SFUP if no scan was performed within 6 weeks. Scans will in include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed. Earlier assessments can be made if clinically indicated at the discretion of the managing physician. If the subject is removed for any reason other than clinically significant disease progression, imaging should be collected during LTFU as long as subject consents to continue.

[redacted]

[g] Safety Follow Up to be performed 30 days (+/- 7 days) after EOT.

[h] Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected

[redacted]

Table 8. Schedule of Assessments-dose escalation Cohort [redacted] Infusion Cycle 1 (Arm 1, AMG 596 Monotherapy)

	Optional Pre-SCR	SCR	Treatment Period - Dose Escalation [redacted] C1																										
Cycle			1																										
Cycle Day		[redacted]																											
	Any time prior to SCR		**Pre-dose**	**Relative to start of infusion**																				**Relative to end of infusion**						
				0.5	**1**	**2**	**3**	**4 (+1)**	**6**	**8**	**12**	**16**	**20**	**24**	**48**									**EOI**	**0.5**	**2**	**4**	**8**	**24**	
GENERAL AND SAFETY ASSESSMENTS																													
Informed consent	X	X																											
Hospitalization[a]			X																				X						
Medical History		X																											
Concomitant Medications		X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Serious adverse events		X	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Adverse events [i]			X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Clinical Evaluation[b]		X	X											X	X	X	X	X	X	X	X	X	X						X	X
Neurological Evaluation		X	X												X		X		X		X		X							X
Vital signs, pulse oximetry[c]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						X	X
ECG triplicate measurement		X	X												X								X							
LABORATORY ASSESSMENTS																													
Serum pregnancy test[d]		X	X																										
Coagulation		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
Blood Glucose Test		X	X						X					X	X	X	X	X	X	X	X	X	X							X
Cytokines / CRP (local lab)		X	X						X					X	X	X	X	X	X	X	X	X	X						X	X
Urinalysis/Dipstick		X	X												X		X		X		X		X							X
Hepatitis Serology, HIV, HLA		X																											
[redacted]																													
INVESTIGATIONAL PRODUCT DOSING																													
AMG 596	[redacted]																												
BIOMARKER ASSESSMENTS																													
[redacted]																													
DISEASE ASSESSMENTS																													
Imaging [e]		X																											
Treatment response																													X

Footnote defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycle 1 will be for a minimum of 7 days from the start of the infusion, and for at least 24 hours following completion of the infusion, and for 72 hours after a dose step at cycle 1 (if applicable).

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and following this every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

[h] If a subject discontinues after C1 this visit assessments will be considered EOT assessments. After EOT, please perform SFUP assessments as in Table 9 Dose Escalation Cohort [redacted] Infusion Cycle 2 and all subsequent cycles.

[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

Table 9. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 2, and all Subsequent Cycles (Arm 1, AMG 596 Monotherapy)

	Treatment Period - Dose Escalation [redacted] C2 and subsequent cycles																											
Cycle	2 and all subsequent cycles																											
Cycle Day	[redacted]																											
		Relative to start of infusion																		Relative to EOI								Every 3 months (2+/- weeks)
	Pre-dose	0.5	1	2	3	4	6	8	12	16	20	24	48							EOI	0.5	2	4	24				
GENERAL AND SAFETY ASSESSMENTS																												
Informed consent																												
Hospitalization[a]								X																				
Concomitant Medications	X	→																										→
Serious adverse events	X	→																										→ X[j]
Adverse events	X	→																										→
Clinical Evaluation[b]	X											X	X	X	X	X	X	X	X	X	X				X[f]	X	X	X	
Neurological Evaluation	X												X		X		X		X		X					X	X	X	
Vital signs, pulse oximetry[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					X[f]	X	X	X	
ECG triplicate measurement	X												X							X							X	X	
LABORATORY ASSESSMENTS																												
Serum pregnancy test[d]	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	
Blood Glucose Test	X						X					X	X	X	X	X	X	X	X	X	X					X	X	X	
Cytokines / CRP (local lab)	X						X					X	X	X	X	X	X	X	X	X	X				X[f]	X	X	X	
Urinalysis/Dipstick	X												X		X		X		X	X	X					X	X	X	
Hepatitis Serology, HIV																												
[redacted]																												
INVESTIGATIONAL PRODUCT DOSING																												
AMG 596	[redacted]																											
BIOMARKER ASSESSMENTS																												
[redacted]																												
DISEASE ASSESSMENTS																												
Imaging[e]																									X		X	X
Treatment response																									X		X	X

Footnote defined on the next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycle 2 and all subsequent cycles and after dose step (if applicable) at cycle 2 and all subsequent cycles will be for a minimum of 72 hours until cycle 5 and 48 hours from cycle 6 onwards (per treating investigator's discretion).

[b] Clinical evaluations will include physical exam, ECOG, and weight.

[c] Vital Signs will be repeated every 4 hours during the first 24 hours of infusion and following this every 6 hours during the minimum hospitalization period in each cycle (see footnote a). Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed every 10 to 12 weeks from start of treatment, and at SFUP if no scan was performed within 6 weeks. Scans will in include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed. Earlier assessments can be made if clinically indicated at the discretion of the managing physician. If the subject is removed for any reason other than clinically significant disease progression, imaging should be collected during LTFU as long as subject consents to continue.

[redacted]

[g] Safety Follow Up to be performed 30 days (+/- 7 days) after EOT.

[redacted]

[j] Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected.

Table 10. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 1 (Arm 2, Combination Therapy)

	Optional Pre-SCR		SCR		Treatment Period-Dose Escalation [redacted] AMG 596 Cycle1 (AMG 404 1st and 2nd Infusion)																										
Cycle -Day	[redacted]																														
	Any time Prior to SCR		Pre-Dose(hr)		Hours Relative to Start of AMG 596 Infusion																				Hours Relative to End of AMG 596 Infusion							
				0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48										EOI	0.5	2	4	8	24		
INVESTIGATIONAL PRODUCT DOSING																															
AMG 596	[redacted]																														
AMG 404																															
Hours Relative to AMG 404 Infusion																															
GENERAL SAFETY ASSESSMENT																															
Informed Consent	X	X																													
Hospitalization[a]												X																			
Medial History		X																													
Concomitant Medications		X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events		X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse Events[l]			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Ealuation[b]		X	X											X	X	X	X				X	X	X	X	X	X				X	X	
Neurological Evatluation		X	X												X		X					X		X		X					X	
Vital signs, pulse oximetry[c]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X				X	X	
ECG triplicate		X	X					X							X		X	X		X						X				X	
LABORATORY ASSESSMENT																															
Serum Pregnancy Test[d]		X	X																												
Coagulation		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	
Blood Glucose Test		X	X						X					X	X	X	X				X	X	X	X	X	X					X	
Cytokines/CRP(Local Lab)		X	X						X					X	X	X	X				X	X	X	X	X	X				X	X	
Urinalysis/Dipstick		X	X												X		X					X		X		X					X	
Hetatitis Serology, HIV, HLA		X																													
[redacted]																															
ACTH, ANA, ANCA[k]		X															X														

Page 1 of 2

Footnotes defined on next page of the table

Table 10. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 1 (Arm 2, Combination Therapy)

	Optional Pre-SCR		SCR		Treatment Period-Dose Escalation [redacted] AMG 596 Cycle1 (AMG 404 1st and 2nd Infusion)																											
Cycle -Day	[redacted]																													
	Any time Prior to SCR		Pre-dose(hr)		Hours Relative to Start of AMG 596 Infusion																			Hours Relative to End of AMG 596 Infusion							
				0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48											EOI	0.5	2	4	8	24		
INVESTIGATIONAL PRODUCT DOSING																														
AMG 596	[redacted]																													
AMG 404																														
Hours Relative to AMG 404 Infusion																														
BIOMARKER ASSESSMENTS																														
[redacted]																														
DISEASE ASSESSMENTS																														
Imaging[e]		X																												

Footnotes defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycle 1 will be for a minimum of 8 days from the start of the AMG 596 infusion, whereby AMG 404 will be administered on [redacted] and for at least 24 hours following completion of the AMG 596 infusion. All subjects will be hospitalized for at least 72 hours after a dose step of AMG 596 at cycle 1 (if applicable). Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

[h] If a subject discontinues after C1 this visit assessments will be considered EOT assessments. After EOT, please perform SFUP assessments as in Table 11

[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

[k] ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

Table 11. Schedule of Assessments Dose Escalation Cohort [redacted] AMG 596 Cycle 2 (AMG 404 3rd Infusion), Cycle 4 and all Subsequent Even Number Cycles (Arm 2, Combination Therapy)

Treatment Period-Dose Escalation [redacted] AMG 596 Cycle 2 (AMG 404 3rd infusion), Cycle 4, and all Subsequent Even Number Cycles																														
Cycle -Day		[redacted]																												
	Pre-Dose(hr)	Hours Relative to Start of AMG 596 Infusion																			Hours Relative to End of AMG 596 Infusion									Every 3 Months (+/- 2 weeks)
		0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48								EOI	0.5	2	4	8	24				
INVESTIGATIONAL PRODUCT DOSING																														
AMG 596		[redacted]																												
AMG 404																														
Hours Relative to AMG 404 Infusion																														
GENERAL AND SAFETY ASSESSMENT																														
Informed Consent																														
Hospitalization[a]								X														X								
Medial History																														
Concomitant Medications	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Adverse Events[i]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Ealuation[b]	X											X	X	X	X	X	X	X	X			X		X			X	X	X	X
Neurological Evatluation	X												X		X		X		X								X	X	X	X
Vital signs, pulse oximetry[C]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			X	X	X	X
ECG triplicate Measurement	X					X							X						X	X									X	X
LABORATORY ASSESSMENT																														
Serum Pregnancy Test[d]	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
Blood Glucose Test	X						X					X	X	X	X	X	X	X	X		X	X						X	X	X
Cytokines/CRP	X						X					X	X	X	X	X	X	X	X		X	X					X	X	X	X
Urinalysis/Dipstick	X												X		X		X					X						X	X	X
Hetatitis Serology, HIV, HLA																														
[redacted]																														
ACTH, ANA, ANCA[k]																			X											

Footnotes defined on next page of the table

Table 11. Schedule of Assessments Dose Escalation Cohort [redacted] AMG 596 Cycle 2 (AMG 404 3rd Infusion), Cycle 4 and all Subsequent Even Number Cycles (Arm 2, Combination Therapy)

Treatment Period-Dose Escalation [redacted] AMG 596 Cycle 2 (AMG 404 3rd infusion), Cycle 4, and all Subsequent Even Number Cycles																																
Cycle -Day		[redacted]																														
	Pre-dose(hr)		Relative to start of AMG 596 infusion																		Relative to End of AMG 596 Infusion										Every 3 Months (+/- 2 weeks)
		0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48									EOI	0.5	2	4	8	24				
INVESTIGATIONAL PRODUCT DOSING																																
AMG 596	[redacted]																															
AMG 404																																
Hours relative to AMG 404 Iinfusion																																
BIOMARKER ASSESSMENTS																																
[redacted]																																
DISEASE ASSESSMENT																																
Imaging[e]																												X		X	X	
Treatment Response																												X		X	X	

Footnotes defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] For combination therapy, Hospitalization at start of AMG 596 cycle 2 and all subsequent cycles, and after dose step (if applicable) at cycle 2 and all subsequent cycles, will be for a minimum of 72 hours after start of AMG 596 until cycle 5. Hospitalization will be at minimun of 48 hours after start of AMG 596 from cycle 6 onwards (per investigator's discretion)., Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

[j] Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected.

[k] ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

Table 12. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 3, and all Subsequent Odd Number Cycles (Arm 2, Combination Therapy)

			Treatment Period-Dose Escalation [redacted] AMG 596 Cycle 3, and all subsequent Odd Number Cycles																											
Cycle -Day	[redacted]																													
	Pre-dose(hr)		Hours Relative to Start of AMG 596 Infusion																		Hours Relative to End of AMG 596 Infusion									Every 3 Months (+/- 2 weeks)
		0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48								EOI	0.5	2	4	8	24					
INVESTIGATIONAL PRODUCT DOSING																														
AMG 596	[redacted]																													
AMG 404																														
Hours Relative to AMG 404 Infusion																														
GENERAL SAFETY ASSESSMENT																														
Informed Consent																														
Hospitalization[a]									X												X						X			
Medial History																														
Concomitant Medications	X	→																												→
Serious Adverse Events	X	→																												→
Adverse Events[i]	X	→																												→
Clinical Ealuation[b]	X											X	X	X	X		X	X	X	X	X	X				X	X		X	
Neurological Evatluation	X												X		X				X		X		X						X	
Vital signs, pulse oximetry[C]	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X							X	
ECG triplicate Measurement	X					X							X		X	X					X						X	X	X	X	
LABORATORY ASSESSMENT																														
Serum Pregnancy Test[d]	X																													
Coagulation	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
Blood Glucose Test	X						X					X	X	X	X		X	X	X	X	X						X		X	X
Cytokines/CRP (Local lab)	X						X					X	X	X	X		X	X	X	X	X					X	X		X	X
Urinalysis/Dipstick	X												X		X			X		X	X						X		X	X
Hetatitis Serology, HIV, HLA																														
[redacted]																														
ACTH, ANA, ANCA[k]															X															

Footnotes defined on next page of the table

Table 12. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 3, and all Subsequent Odd Number Cycles (Arm 2, Combination Therapy)

			Treatment Period-Dose Escalation [redacted] AMG 596 Cycle 3, and all Subsequent Odd Number Cycles																												
Cycle -Day		[redacted]																													
	Pre-dose(hr)		Relative to start of AMG 596 infusion																Relative to End of AMG 596 Infusion											Every 3 Months (+/- 2 weeks)
		0.5	1	2	3	4(+1)	6	8	12	16	20	24	48									EOI	0.5	2	4	8	24					
INVESTIGATIONAL PRODUCT DOSING																															
AMG 596	[redacted]																														
AMG 404																															
Hours Relative to AMG 404 Infusion																															
GENERAL SAFETY ASSESSMENT																															
[redacted]																															
DISEASE ASSESSMENT																															
Imaging[e]																												X		X	X
Treatment Response																												X		X	X

Footnotes defined on next page of the table

[a] For combination therapy, hospitalization at start of AMG 596 cycle 2 and all subsequent cycles, and after dose step (if applicable) at cycle 2 and all subsequent cycles, will be for a minimum of 72 hours after start of AMG 596 until cycle 5. Hospitalization will be at minimun of 48 hours after start of AMG 596 from cycle 6 onwards (per investigator's discretion)., Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and following this every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

[k] ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

Table 13. Schedule of Assessments Dose Expansion Cohort 28-day Infusion Cycle 1 (Arm 1, AMG 596 Monotherapy)

	Optional Pre-SCR	SCR	Treatment Period - Dose Expansion																				
Cycle			1																				
Cycle Day	Any time prior to SCR		Pre-dose	Relative to start of infusion																		EOI	
				0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48								
GENERAL AND SAFETY ASSESSMENTS																							
Informed consent	X	X																					
Hospitalization[a]									X														
Medical History		X																					
Concomitant Medications		X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Serious adverse events		X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Adverse events [i]			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Clinical Evaluation[b]		X	X											X	X	X	X	X	X	X	X	X	X
Neurological Evaluation		X	X												X							X	
Vital signs, pulse oximetry[c]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG triplicate measurement		X	X												X							X	
LABORATORY ASSESSMENTS																							
Serum pregnancy test[d]		X	X																				
Coagulation		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
Blood Glucose Test		X	X						X					X	X	X	X	X	X	X	X	X	X
Cytokines / CRP (local lab)		X	X						X					X	X	X	X	X	X	X	X	X	X
Urinalysis/Dipstick		X	X												X		X		X		X	X	X
Hepatitis Serology, HIV, HLA		X																					
[redacted]																							
INVESTIGATIONAL PRODUCT DOSING																							
AMG 596	[redacted]																						
BIOMARKER ASSESSMENTS																							
[redacted]																							
DISEASE ASSESSMENTS																							
Imaging [e]		X																					
Treatment response																							X

Footnotes defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycle 1 will be for a minimum of 7 days from the start of the infusion, and for at least 24 hours following completion of the infusion, and for 72 hours after a dose step at cycle 1 (if applicable).

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and following this every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

[g] If a subject discontinues after C1 this visit assessments will be considered EOT assessments. After EOT, please perform SFUP assessments as in Table 14

[redacted]

[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

Table 14. Schedule of Assessments Dose Expansion Cohort [redacted] Infusion Cycle 2 and all Subsequent Cycles (Arm 1, AMG 596 Monotherapy)

	Treatment Period - Dose Expansion																							
Cycle	2 and all subsequent cycles																							
Cycle Day	[redacted]																							
	Pre-dose	Hours Relative to Start of AMG 596 Infusion																		EOI				Every 3 months (+/- 2 weeks)
		0.5	1	2	3	4	6	8	12	16	20	24	48											
GENERAL AND SAFETY ASSESSMENTS																								
Informed consent																								
Hospitalization[a]								X																
Concomitant Medications	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Serious adverse events	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶ X[h]
Adverse events	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	▶
Clinical Evaluation[b]	X										X	X	X	X	X	X	X	X	X	X	X	X	X	
Neurological Evaluation	X											X		X		X		X			X	X	X	
Vital signs, pulse oximetry[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG triplicate measurement	X											X								X		X	X	
LABORATORY ASSESSMENTS																								
Serum pregnancy test[d]	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	
Blood Glucose Test	X						X				X	X	X	X	X	X	X	X	X	X	X	X	X	
Cytokines / CRP (local lab)	X						X				X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis/Dipstick	X											X		X		X		X		X	X	X	X	
Hepatitis Serology, HIV																								
[redacted]																								
INVESTIGATIONAL PRODUCT DOSING																								
AMG 596	[redacted]																							
BIOMARKER ASSESSMENTS																								
[redacted]																								
DISEASE ASSESSMENTS																								
Imaging[e]																					X		X	X
Treatment response																					X		X	X

Footnotes defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of cycle 2 and all subsequent cycles and after dose step at cycle 2 and all subsequent cycles (if applicable) will be for a minimum of 72 hours until cycle 5 and 48 hours from cycle 6 onwards (per treating investigator's discretion).

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed every 10 to 12 weeks from start of treatment, and at SFUP if no scan was performed within 6 weeks. Scans will in include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed. Earlier assessments can be made if clinically indicated at the discretion of the managing physician. If the subject is removed for any reason other than clinically significant disease progression, imaging should be collected during LTFU as long as subject consents to continue.

[f] Safety Follow Up to be performed 30 days (+/- 7 days) after EOT.

[redacted]

[h] Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected.

Table 15. Schedule of Assessment Dose Expansion Cohort [redacted] Cycle 1 and all Subsequent Odd Number Cycles (Arm 2, Combination Therapy)

	Optional Pre-SCR	SCR	Treatment Period-Dose Expansion Cohorts-Cycle 1, Cycle3, and all Subsequent Odd Number Cycles																							
Cycle Day	[redacted]																									
			Pre-dose	Hours Relative to Start of AMG 596 Infusion																				EOI		
				0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48											
INVESTIGATIONAL PRODUCT DOSING																										
AMG 596	[redacted]																									
AMG 404																										
Hours Relative to MAG 404 Infusion																										
GENERAL AND SAFETY ASSESSMENTS																										
Informed Consent	x	X																								
Hospitalization[a]												x														
Medial History		X																								
Concomitant Medications		X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Serious Adverse Events		X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Adverse Events[i]			X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Clinical Evaluation[b]		X	X											X	X	X	X		X	X	X	X	X	X	X	
Neurological Evaluation		X	X												X									X		
Vital Signs, Pulse Oximetry[C]		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG Triplicate Measurement		X	X												X		X	X	X	X		X		X	X	X
LABORATORY ASSESSMENTS																										
Serum Pregnancy Test[d]		X	X																							
Coagulation		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	
Blood Glucose Test		X	X						X					X	X	X	X		X	X	X	X	X	X	X	
Cytokine/CRP (Local lab)		X	X						X					X	X	X	X		X	X	X	X	X	X	X	
Urinalysis/Dipstick		X	X												X		X		X			X		X	X	
Hepatitis Serology, HIV, HLA		X																								
[redacted]																										
ACTH, ANA, ANCA[k]																	X									

Footnotes defined on next page of the table

Table 15. Schedule of Assessment Dose Expansion Cohort [redacted] Cycle 1 and all Subsequent Odd Number Cycles (Arm 2, Combination Therapy)

	Optional Pre-SCR	SCR	Treatment Period-Dose Expansion Cohorts-Cycle 1, Cycle3, and all Subsequent Odd Number Cycles																							
Cycle Day	[redacted]																									
			Pre-dose	Hours Relative to Start of AMG 596 Infusion																				EOI		
				0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48											
INVESTIGATIONAL PRODUCT DOSING																										
AMG 596	[redacted]																									
AMG 404																										
Hours Relative to MAG 404 Infusion																										
BIOMARKER ASSESSMENTS																										
[redacted]																										
DISEASE ASSESSMENTS																										
Imaging[e]		X																								
Treatment Response																									X	

Footnotes defined on next page of the table

EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up

[a] Hospitalization at start of AMG 596 cycle 1 will be for a minimum of 8 days from the start of the AMG 596 infusion, whereby AMG 404 will be administered on [redacted], and for at least 24 hours following completion of the AMG 596 infusion. All subjects will be hospitalized for at least 72 hours after a dose step of AMG 596 at cycle 1 (if applicable). Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

[g] If a subject discontinues after C1 this visit assessments will be considered EOT assessments. After EOT, please perform SFUP assessments as in Table 16.

[redacted]

Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

[j] ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

Table 16. Schedule of Assessment Dose Expansion cohort [redacted] Cycle 2 and all Subsequent Even Number Cycles (Arm 2, Combination Therapy)

	Treatment Period-Dose Expansion Cohorts-Cycle 2 and all Subsequent Odd Number Cycles																										
Cycle Day	[redacted]																										
	Pre-dose	Hours Relative to Start of AMG 596 Infusion																									Every 3 months (+/-2 weeks)
		0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48										EOI	24				
INVESTIGATIONAL DRUG DOSING																											
AMG 596	[redacted]																										
AMG 404																											
Hours Relative to AMG 404 Infusion																											
GENERAL AND SAFETY ASSESSMENTS																											
Informed Consent																											
Hospitalization[a]									X																		
Conconmitant Medications	X	→																									
Sevious Adverse Events	X	→																									X[j]
Adverse Events[i]	X	→																									
Clinical Evaluation[b]	X											X	X	X	X	X	X	X	X			X	X	X	X	X	
Neurological Evaluation	X												X		X		X		X				X	X	X	X	
Vital Signs, Pulse Oximetry[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG Triplicate Measurement	X					X							X						X	X		X			X	X	
LABORATORY ASSESSMENTS																											
Serum Pregnancy Test[d]	X																										
Cogulation	X											X	X	X	X				X		X	X		X	X	X	
Hematology, Chemistry	X											X	X	X	X				X		X	X		X	X	X	
Blood Glucose Test	X						X					X	X	X	X				X		X	X		X	X	X	
Cytokines/ CRP (local Lab)	X						X					X	X	X	X				X		X	X	X	X	X	X	
Urianalysis/Dipstick	X												X		X				X			X		X	X	X	
Hepatatis Serology, HIV, HLA																											
[redacted]																											
ACTH, ANA, ANCA[k]																			X								

Footnotes defined on next page of the table

Table 16. Schedule of Assessment Dose Expansion cohort [redacted] Cycle 2 and all Subsequent Even Number Cycles (Arm 2, Combination Therapy)

	Treatment Period-Dose Expansion Cohorts-Cycle 2 and all Subsequent Odd Number Cycles																										
Cycle Day	[redacted]																										
	Pre-Dose	Hours Relative to start of AMG 596 Infusion																									Every 3 months (+/-2 weeks)
		0.5	1	2	3	4 (+1)	6	8	12	16	20	24	48									EOI	24				
INVESTIGATIONAL DRUG DOSING																											
AMG 596		X																									
AMG 404																		X									
Hours Relative to AMG 404 Infusion																		Pre-Dose	EOI								
BIOMARKER ASSESSMENTS																											
[redacted]																											
DISEASE ASSESSMENTS																											
Imaging[e]																										X	X
Treatment Response																								X		X	X

Footnotes defined on next page of the table

[a] For combination therapy, hospitalization at start of AMG 596 cycle 2 and all subsequent cycles, and after dose step (if applicable) at cycle 2 and all subsequent cycles, will be for a minimum of 72 hours after start of AMG 596 until cycle 5. Hospitalization will be at minimun of 48 hours after start of AMG 596 from cycle 6 onwards (per investigator's discretion)., Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards

[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.

[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.

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

[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.

[redacted]

Safety Follow Up to be performed 30 days (+/- 7 days) after EOT.

[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.

[j] Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected.

[k] ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.

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 14 days of day 1, 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 (Section 7.1, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15 and Table 16).

AMG 596 dose step can be introduced on [redacted] of a cycle, and assessments for the first week of the step dose ([redacted]) must follow assessments for [redacted] of a cycle except for the pregnancy test. In case of step dosing, AMG 404 will be administered [redacted] after the AMG 596 target dose is achieved in cycle 1.

AMG 404 will be given every [redacted] ECG triplicate measurements will be performed during first AMG 404 infusion at predose, EOI, and 4 hours after end of infusion for cycle 1. In all subsequent AMG 404 dose, ECG triplicate measurements will only be collected at predose and EOI.

Subjects will be seen in the clinic for study evaluations. When electrocardiograms (ECGs), vital signs, blood sample collections, biomarker 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 catheter port used for AMG 596 or AMG 404 infusion. If a permanent central line with more than one lumen is used, blood draws can be done via the lumen that is not used for drug administration. The time of blood sample collection must be recorded with the exact time of collection in the subject's medical records and in the eCRF (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 provide additional details regarding the requirements for these procedures.

Acceptable deviation windows are as follows:

- After completion of cycle 1 (AMG 596 and AMG 404), +/- 1 day for all visits if logistically necessary
- ECGs, biomarker [redacted] vital signs (incl. pulse oximetry):
  - ± 15-minute window if collected within the first 24 hours (excluding the 24-hour sample) after the start of an infusion (or dose step, if applicable).
  - ± 2-hour window if collected between 24 hours and 3 days after the start of an infusion (or dose step, if applicable).
  - Assessments after day 3 should be performed on the indicated study day, but not at a certain hour of the day.
  - ± 1day window if collected at D8 or later, or at the EOI.
- PK blood draws in cycles 1 - 3:
  - within two hours prior to treatment start / dose step (if applicable)
  - ± 15-minute window for samples taken within the first 24 hours after start of infusion and within 24 hours after EOI. In case of a dose step, the ± 15-minute window also applies to the samples taken within the first 24 hours after dose step.

Local laboratories should be used for the following assessments: hematology, clinical chemistry including cytokines, coagulation, urinalysis, hepatitis serology, HIV, and serum pregnancy tests. Additional parameters can be explored locally and centrally for safety evaluations. The following collections will be shipped to a central laboratory for analysis: blood samples for determination of plasma concentrations of [redacted]. Refer to the laboratory manual for detailed collection, processing, and shipping procedures.

Table 17. List of Analytes

Chemistry	Hematology	Coagulation	Urinalysis	Other
Sodium Potassium Chloride Bicarbonate (HCO3) or carbon dioxide Total protein Albumin Calcium Calcium corrected Glucose Blood urea nitrogen or Urea Creatinine Estimated CrCl GFR, MDRD calculation Total creatine kinase Total bilirubin (TBL) Direct bilirubin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) TSH*** Free T4***	RBC Hemoglobin Hematocrit Mean corpuscular volume (MCV) Platelets White blood cell differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	PT PTT INR Fibrinogen AT III	Specific gravity pH Blood Protein Glucose BilirubinMicroscopic exam** (performed at the discretion of the Investigator)	C-reactive protein (CRP) IL-6 Serum Pregnancy HLA typing Hepatitis B surface antigen Hepatitis C antibody HIV* ACTH*** ANA*** ANCA*** (cytoplasmic and perinuclear)

* Hepatitis B surface antigen, Hepatitis C antibody, PCR for Hepatitis C RNA (if Hepatitis C antibody is positive), and HIV assessments are recommended.
** WBC, RBC, Epithelial Cells, Bacteria, Casts, and Crystals
*** Only applicable for AMG 404 infusion
ACTH = Adrenocorticotropic hormone; ANA = Antinuclear Antibodies; ANCA = Antineutrophil cytoplasmic antibodies;

A serum pregnancy test will be performed locally at each site on all female 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.

Additional procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion. This may include measurement of urine output, if deemed appropriate by the Investigator.

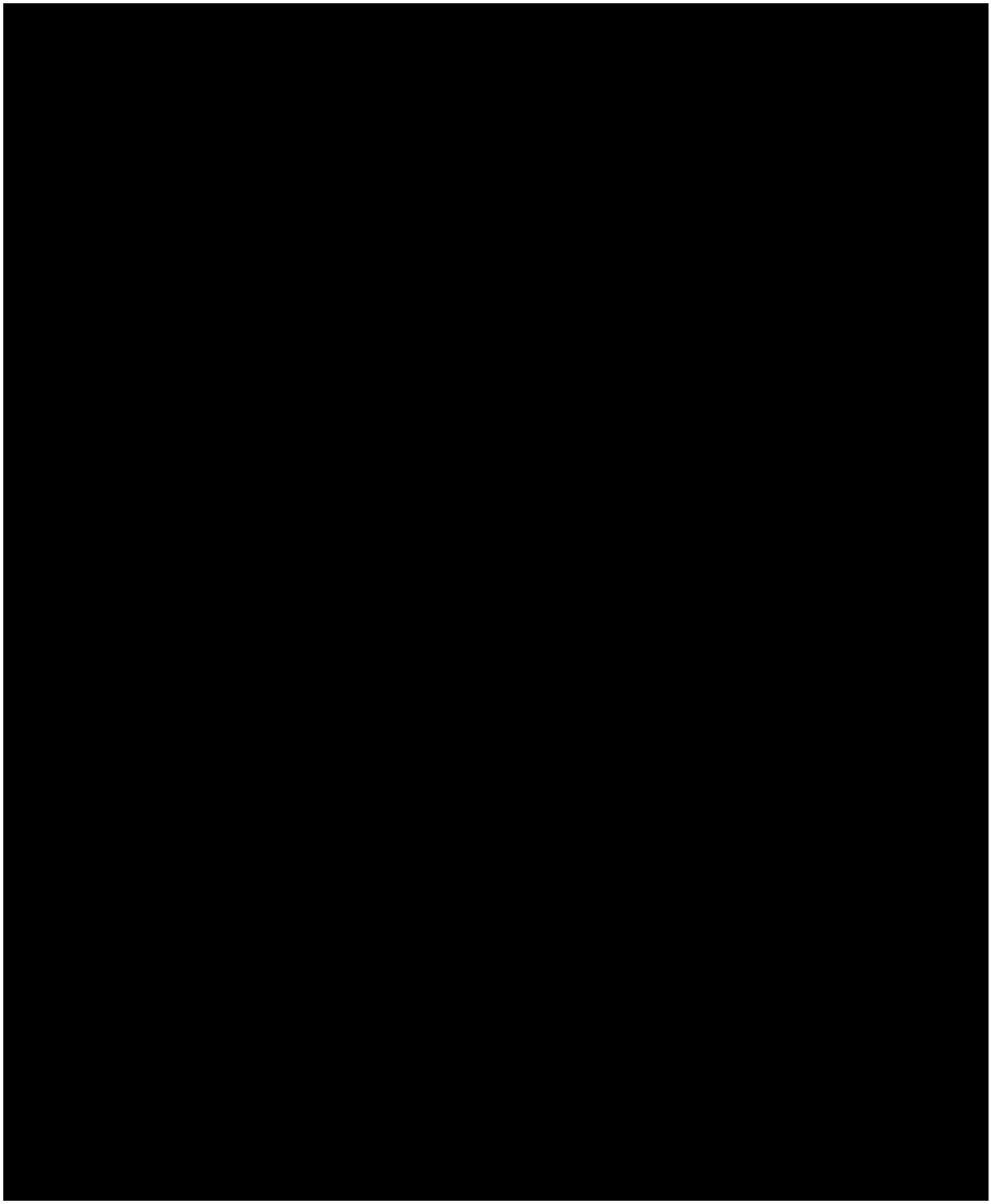
7.2.1 Pre-Screening and Screening

The pre-screening evaluation is optional and serves to pre-determine EGFRvIII-positivity. Up to 500 subjects diagnosed with glioblastoma or malignant glioma may undergo the pre-screening evaluation. Pre-screening can start after written informed consent for pre-screening has been obtained and should be completed prior to signing consent for study participation.

[redacted] After EGFRvIII-positivity has been reported and prior to signing consent for study participation, the subject may still receive one or more antitumor-treatments. During pre-screening, investigators may also provide the results of EGFRvIII positive testing from local testing for trial enrollment. If prescreening is used for enrollment, then plasma must be collected at screening or pre-dose for confirmation of mutation status when the plasma assay is ready. When the plasma test is ready, then patients will be enrolled using this plasma assay.

Subjects may also enter directly into the screening period without pre-screening.

[redacted]



The following assessments will be completed during Screening:

- Confirmation that the ICF for participation in the study has been signed
- Demographic data including sex, age, 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. Physical examination findings should be recorded on the appropriate eCRF
  - Medical/surgical history (medical history data becoming available after the screening period will also have to be collected)
    - Including renal/urinary history (including urine output)
  - ECOG performance status
  - Height and weight
- Neurological Evaluation
- 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, and HIV, cytokines/CRP, blood glucose test
- Biomarker assessments: [redacted]
- Note: Test results confirming EGFRvIII positivity expire with start of any antitumor therapy between re-screenings and need to be repeated in this case.
- Imaging assessment collected at screening visit
- Data from prior imaging evaluation (historical imaging) within 6 months of enrollment.
- 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 as of signature of the informed consent should be collected. For prior therapies, collect therapy name, indication, dose, unit, frequency, start date, and stop date.

7.2.2 Treatment

All subjects will be hospitalized for the following periods:

Cycle 1:

- For the first [redacted] of AMG 596 monotherapy (Arm 1)
- For the first [redacted] of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on [redacted]
- For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2
- For additional 72 hours after AMG 596 step dose if necessary

Cycle 2 and all subsequent cycles:

- For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2
- For additional 72 hours after AMG 596 step dose if necessary.

Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator.

AMG 404 can be administered in an outpatient setting starting from cycle 1 [redacted] onwards. Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.

Restart of the infusion should be performed in the clinic/hospital under the supervision of the investigator or designee and the subject should be hospitalized for a minimum of 24 hours when the infusion interruption meets the following criteria:

- associated to an AE, or
- interruption > 24 hours due to a pump related issue.

Dosing with AMG 596 or AMG 596 in combination with AMG 404 can continue unless the subject becomes intolerant to investigational product, the signs and symptoms of clinical progression are evident as determined by the investigator, or the subject withdraws consent. Tumor evaluations by MRI will occur every 10 to 12 weeks from start of treatment. Earlier assessments can be made if clinically indicated at the discretion of the managing physician. Modified RANO criteria (Appendix D) will be used allowing subjects to stay on study until clinically significant disease progression if no other treatment discontinuation criteria apply. Upon discussion with the Sponsor, subjects may continue to receive treatment after radiographic confirmation of progressive disease as long as they continue to derive clinical benefit in the opinion of the investigator and until further increase in tumor burden. For analysis purposes, date of PD is the date of initial observed PD.

Investigational product is to be administered after all other protocol required pre-dose assessments have been performed on day 1 of each cycle.

The results from laboratory tests taken on day prior to infusion start do not have to be available before start of treatment with AMG 596. Laboratory assessments completed within 24 hours prior to treatment start do not have to be repeated on day 1 prior to infusion start.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Section 7.1). Treatment period starts when

the first cIV infusion of AMG 596 is administered to a subject. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments.

- Hospitalization
- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Weight
- Neurological Evaluation
- 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), blood glucose test, cytokines/CRP
- Biomarker assessments: [redacted]
- [redacted]
- Imaging Assessment
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications

7.2.3 End of Treatment (EOT)

The EOT visit will occur upon documented clinically significant disease progression, intolerable adverse event, or withdrawal of consent (see Section 8) for a complete list of reasons for permanent treatment discontinuation. 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 that are considered related to the investigational product 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 (Section 7.1):

- Clinical evaluation
  - Physical examination as per standard of care Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Weight
- Neurological evaluation
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurement
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, blood glucose test, cytokines/CRP
- Biomarker assessments: [redacted]
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications

7.2.4 Safety Follow Up Visit

The safety follow-up visit (SFUP) is to be performed 30 days (+/- 7 days) after the last dose of AMG 596 and AMG 404 even if the subject begins another therapy. All efforts should be made to conduct this visit. If it is not possible to conduct the SFUP 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 SFUP visit as designated in the Schedules of Assessments (Section 7.1)

- Clinical evaluation
  - Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate eCRF.
  - ECOG performance status
  - Weight
- Neurological evaluation
- Vital signs (ie, blood pressure, heart rate, respiratory rate, and temperature)
- Pulse oximetry
- ECG triplicate measurements
- Laboratory assessments: hematology, chemistry, coagulation, urinalysis, blood glucose test, cytokines/CRP

- Biomarker assessments: [redacted]
- [redacted]
- Imaging assessment if last assessment was done more than 6 weeks prior to this visit
- Treatment response (not applicable to Cohort [redacted])
- Serious adverse event reporting
- Adverse event reporting
- Documentation of concomitant and rescue medications

7.2.5 Long Term Follow Up

The long term follow up visit (LTFU) is to be performed via clinical visit or telephone every 3 months (+/- 2 weeks) after their SFUP visit and until a maximum of 12 months from start of treatment, until start of a new therapy or until death has been reported, whichever occurs first.

Subjects will allow Amgen continued access to medical records for up to 12 months from start of treatment, so that information related to subject's disease status may be obtained. All efforts should be made to conduct this visit. If it is not possible to conduct the LTFU 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 LTFU visit as designated in the Schedules of Assessments (Section 7.1):

- Method of contact (clinical study visits or telephone contact)
- Adverse Events and Serious Adverse Events with respective Concomitant Medications
- Imaging assessments (if collected as part of SoC) and treatment response (if available)

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 and through screening until start of treatment. 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 renal/urinary history (including urine output), 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 glioblastoma or malignant glioma 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 to the SFUP. Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected. Collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.3.5 Weight Measurements

Weight in kilograms should be measured without shoes.

7.3.6 Height Measurements

Height in centimeters should be measured without shoes at screening only.

7.3.7 Vital Signs

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

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.

7.3.8 Pulse Oximetry

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

7.3.9 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, approximately 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 pre-dose 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.

7.3.10 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 (Section 7.1, Table 6, Table 7,

Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, and Table 16.

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.

7.3.11 Eastern Cooperative Oncology Group (ECOG)

Subjects will be graded according to the Eastern Cooperative Oncology Group (ECOG) Performance Status. The ECOG criteria for this protocol are further defined in Appendix F.

7.3.12 Clinical Laboratory Tests

The tests listed Table 17 (List of Analytes) will be conducted on samples collected and analyzed by standard laboratory procedures at the time points specified in the Schedule of Assessments (Section 7.1, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12,Table 13, Table 14, Table 15 and Table 16). 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.

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.

7.3.13 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 596) must be discontinued. If the quantitative pregnancy test is negative the subject should restart infusion per the criteria in Section 6.2.4.

7.3.14 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. Determination of the severity of all adverse events will be consistent with the CTCAE, version 4.0 (Appendix A) unless specified otherwise.

7.4 Pharmacokinetic Blood Sampling

Blood samples will be obtained for determination of serum concentrations of AMG 596 in the monotherapy and for the determination of serum concentrations of AMG 596 and AMG 404 in the combination therapy at the time points specified in the Schedules of Assessments (Section 7.1, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12,Table 13, Table 14, Table 15 and Table 16). Blood must not be drawn from the port catheter. Sample collection, processing, storage, and shipping instructions are provided in a separate laboratory manual.

[redacted]

[redacted]

7.8 Sample Storage and Destruction

Any blood, tissue or CSF sample collected according to the Schedule of Assessments (Section 7.1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand glioblastomas and malignant gliomas, the dose response and/or prediction of response to AMG 596 and in combination with AMG 404, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

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

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

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

7.9 Imaging Assessment of Disease Burden

7.9.1 Magnetic Resonance Imaging (MRI)

MRI of the brain will be done at screening, every 10 to 12 weeks from start of treatment and at SFUP or until the signs and symptoms of clinical progression are evident as determined by the investigator, radiographic progression is confirmed in 2 scans ≥ 4 weeks apart without signs of clinical benefit, start of a new treatment, death or the subject withdraws consent (see Section 7.1 Schedule of Assessment). Upon discussion with the Sponsor, subjects may continue to receive treatment after radiographic confirmation of progressive disease as long as they continue to derive clinical benefit and until further increase in tumor burden. For analysis purposes, date of PD is the date of initial observed PD. All scans for each subject will be performed in the same manner as at baseline, at the same field strength, preferably on the same scanner. The same contrast agent should be used through the study; macrocyclic gadolinium agents are preferred. Scans should be acquired with a slice thickness ≤ 5 mm. At each imaging timepoint, the following sequences will be performed:

- Axial Pre Contrast (2D) T1
- Axial T2
- Axial T2/FLAIR
- Axial Post Contrast (2D) T1

- Axial diffusion-weighted magnetic resonance imaging (DWI) (at selected sites)
- Sagittal Post Contrast (3D) T1 (selected sites if part of site protocol)

Subjects who demonstrate an objective response or disease progression will have a confirmatory MRI performed at least 4 weeks after the initial observation scan.

7.9.2 Tumor Assessment by MRI

The Response Assessment in Neuro-Oncology (RANO) Working Group published recommendations that extend the Macdonald Criteria, and specifically incorporate T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) sequences to better capture non-enhancing components that may be present in high grade gliomas (Wen et al, 2010). The modified RANO criteria for this protocol are further defined in Appendix D.

Imaging data may be submitted to a central laboratory for archival and/or additional analysis. Additional MRI endpoints reflecting tumor biology, eg, functional diffusion maps and three-dimensional tumor volume, and alternate response criteria, eg, Macdonald, RANO or iRANO, may also be evaluated.

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 can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product, device or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Section 7.1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/ communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease related events, and device related events, as applicable. Subjects who have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the level of follow-up that is agreed to by the subject.

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

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

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

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression confirmed by 2 scans ≥ 4 weeks apart without signs of clinical benefit

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor (eg, product quality issue)
- withdrawal of consent from study
- death
- lost to follow-up
- start of any other antitumor therapy

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-Related Events

Disease-Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

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

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

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

- An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition, or if the investigator believes there is a causal relationship between the investigational product(s)/ study treatment/ protocol-required therapies and disease worsening, this must be reported as an Adverse Event or Serious Adverse Event.

Table 18 outlines the expected Disease-Related Events by System Organ Class.

Table 18. Disease-Related Adverse Events by System Organ Class

System Organ Class	Preferred Term(s)
Gastrointestinal disorders	Nausea Vomiting
Nervous system disorders	Aphasia Brain edema Cognitive impairment[1] Headache Hemiparesis Intracranial pressure increased Lethargy Seizure Sensory loss Visual field defect

HLT = high level term
[1] Represents preferred terms in the Mental impairment (excluding dementia and memory loss) HLT (MedDRA version 19.0).

9.1.2 Adverse Events

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

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

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 Event eCRF.

For situations when an adverse event or serious adverse event is due to glioblastoma or malignant glioma 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 as an adverse event.

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

9.1.3 Serious Adverse Events

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

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

A Disease-Related event is to be reported as a serious adverse event if the event meets at least 1 of the serious criteria above.

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

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

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-Related Events

The investigator is responsible for ensuring that all Disease-Related Events observed by the investigator or reported by the subject that occur after the first dose of investigational medicinal product(s)/ study treatment/ protocol-required therapies through the End of Study are recorded on the Event eCRF as a Disease-Related Event.

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

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as seriousadverse events and recorded and reported per section 9.2.1 and Appendix I.

Disease-related events pre-defined for this study are listed in Table 18.

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

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the End of Study are reported using the Event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity,
- Assessment of relatedness to investigational product, medical devices or other protocol-required therapy, and
- Action taken.

The adverse event grading scale used will be the CTCAE, version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the investigational product, 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?

The investigator must assess whether the adverse event is possibly related to any study mandated activity (eg, administration of investigational product, protocol-required therapies, use of medical 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 administration of investigational product?"

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

or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the dosing interval of the investigational product or the end of study 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 Event eCRF.

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

The investigator must assess whether the serious adverse event is possibly related to the investigational product, medical devices(s), and/or 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. Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is expected to follow reported serious adverse events until stabilization or 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. If specifically requested, the investigator may need to provide additional follow-up information, such as

discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event eCRF.

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

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

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

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

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

In addition to the attributes listed in Section 9.2.2.1, the investigator must also complete the serious adverse event section of the Event eCRF.

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

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 30 days after the last dose of AMG 596 or through 4 months (120 days) after the last dose of AMG 404.

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

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

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

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

In addition to reporting a lactation case during the study, investigators should report lactation cases that occur through 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) Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

- Dose limiting toxicities (DLT), treatment-emergent adverse events, treatment-related adverse events and changes in vital signs, physical examinations, and clinical laboratory tests

Secondary Endpoint(s):

- PK parameters for monotherapy AMG 596 including, but not limited to, average steady-state concentration (C_{ss}), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life (t1/2) for serum AMG 596
- PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (C_{max}), time to achieve C_{max} (t_{max}), and AUC
- PK parameters for AMG 596 dosed in combination with AMG 404 including, but not limited to, average steady-state concentration (C_{ss}), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life (t1/2) for serum AMG 596
- Objective response (OR) as per modified RANO, time to response, response duration and time to progression (TTP); progression free survival (PFS) at 6 and 12 months after treatment initiation with AMG 596 monotherapy or AMG 596 in combination with AMG 404

Exploratory Endpoint(s):

[redacted]

10.1.2 Analysis Sets

Safety Analysis Set

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 one administration of AMG 596.

RANO Evaluable Analysis Set

The RANO Evaluable Analysis Set includes all subjects that are enrolled and receive at least one administration of AMG 596 with measurable disease at enrollment per RANO.

DLT Evaluable Analysis Set

- The DLT Evaluable Analysis Set includes subjects who are DLT-evaluable and will be used to summarize incidence of dose limiting toxicity (DLT) (see Section 3.3 for definition of DLT-evaluable).

10.1.3 Covariates and Subgroups

Due to the small sample size, the impact of baseline characteristics on study outcomes will not be explored, and no subgroup analyses will be performed.

10.2 Sample Size Considerations

It is anticipated that up to 190 subjects will be enrolled in the study. It is anticipated that up to 100 subjects will be enrolled to Arm 1 in this study and up to 90 subjects will be enrolled to Arm 2 in this study.

For Group 1 (recurrent disease), the following are the planned sample sizes.

- In dose escalation, up to 45 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 30 DLT-evaluable subjects to combination Arm 2
- In dose expansion, up to 15 subjects will be enrolled to monotherapy Arm 1 and up to 15 subjects to combination Arm 2.

For Group 2 (maintenance setting), the following are the planned sample sizes.

- In dose escalation, up to 15 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 20 DLT-evaluable subjects to combination Arm 2
- In dose expansion, up to 25 subjects will be enrolled to monotherapy Arm 1 and up to 25 subjects to combination Arm 2

The sample sizes in dose escalation are based on practical considerations and it is consistent with conventional oncology studies with the objective to identify the RP2D/MTD. With 2 subjects per cohort, there is a 19-56% probability of observing at least one DLT for a cohort if the true DLT rate is 10-33% and with 6 subjects per cohort, the probability is 47-91%.

For Group 1 (recurrent disease) in each respective arm (monotherapy and combination), the respective sample sizes of the dose expansion cohorts are based on practical considerations. With 21 subjects treated at the RP2D/MTD (6 from dose escalation and 15 from dose expansion) in an arm, there is a 66% probability of observing an adverse event with 5% incidence rate. For an ORR of 20%, the probability of observing the OR in at least 4 subjects would be 63%. The estimated ORR and exact 80% CI for 4 responses is 19% and 9%-35% respectively.

For Group 2 (maintenance setting) in each respective arm (monotherapy and combination), the sample sizes in the respective dose expansion arm are based on a Bayesian predictive probability design (Lee, 2008). For both arms, the ORR of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. The maximum sample size per arm is 31 subjects (6 from dose escalation and 25 from dose expansion). Futility will be assessed initially after treating 10 subjects for at least 6 months and continuously for each additional subject afterwards. If ORR is lower than

5%, enrollment may be terminated due to futility. The guidelines for early termination due to futility are as follows:

Number of Treated Subjects	Futility Termination Guideline
10	0 responders
19	1 or fewer responders
26	2 or fewer responders
31	3 or fewer responders

With this design, the probability of accepting the treatment is 0.05 (type I error) when ORR=5% and 0.8 (power) when ORR=20%. If the ORR is 5%, the probability of stopping the trial early at the interim with 10 evaluable subjects for futility is 60% and the expected additional subjects to be assessed in dose expansion is 9.6.

During dose expansion and separately for the monotherapy arm (combining data from Groups 1 and 2) and for the combination arm (combining data from Groups 1 and 2), Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. If this threshold is met, enrollment to dose expansion will be halted pending review of safety data by the DLRT. After receiving the DLRT recommendation, Amgen will choose to take one of the following actions.

1) Terminate the trial

2) Amend the protocol to potentially improve the benefit/risk for subjects (eg, increase safety monitoring, modify dose/schedule, mandate premedication)

3) Continue dose expansion without any changes

The stopping rules use a Bayesian approach proposed by Thall, Simon, and Estey (1995) to terminate the study if the posterior probability that the grade 4 or higher treatment-related adverse event rate is greater than 20% is > 80%. The stopping boundaries assume a prior distribution of Beta (0.40, 1.60) are presented in Table 19 and the operating characteristics with pre-specified batch size of 10 new subjects per batch are presented in Table 20. Subjects included in a batch may come from different study groups. The evaluations could occur more frequently if necessary to address emerging safety concerns. The operating characteristics in Table 19 provide the probability of stopping the trial early for given hypothetical true rate of grade 4 or higher treatment-related adverse events, whereas the stopping criteria in Table 20 are based

on situations where the empirical evidence would result in a posterior probability of ≥ 80% that the true grade 4 or higher treatment-related adverse event rate is ≥ 20%.

Table 19. Stopping Boundary for Dose Expansion

Number of subjects	Hold enrollment if observing this many grade 4 or higher treatment-related adverse events
10	≥ 4
20	≥ 6
30	≥ 9
40	Study Complete

Table 20. Operating Characteristics with Batch Size of 10 Subjects

True grade 4 or higher treatment-related adverse event rate	Probability of early stopping of dose expansion	Average dose expansion sample size
0.10	2.0%	39.5
0.15	9.7%	37.6
0.20	25.8%	33.9
0.25	47.7%	28.8
0.30	69.2%	23.4

10.3 Adaptive Design

During dose escalation for both Arm 1 and Arm 2, a two-parameter Bayesian logistic regression model (BLRM, Neuenschwander et al, 2008) is used to guide dose exploration. The MTD target Toxicity Probability Interval (TPI) for DLT is (0.20, 0.33] and TPIs of (0.33, 0.60] and (0.60, 1.00] are defined as excessive and unacceptable, respectively. The design seeks to identify a dose most likely to have a DLT rate in the target TPI, but with overdose control that limits the possibility the dose has an excessive or unacceptable DLT rate (Babb et al, 1998). The DLT endpoint at dose level d_i is assumed to follow a Bernoulli distribution with probability p_i where the logit of p_i increases linearly with the log of the standardized dose in the following 2-parameter logistic model:

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

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

For both Arm 1 and Arm 2 , a bi-variate normal prior distribution (Neuenschwander, Branson and Gsponer; 2008) is used to select for θ = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at the lowest monotherapy planned dose ([redacted] µg/day) is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose ([redacted] µg/day) is 0.05. These values were selected such that pi is 0.05 for the starting dose and 0.25 for the reference dose. Model sensitivity to the prior will also be investigated and in particular the BLRM will be examined using a prior having a lower reference dose (eg, [redacted] µg/day) and using a prior having a higher reference dose (eg, [redacted] µg/day).

10.4 Planned Analyses

10.4.1 Interim Analyses

Arm 1

In dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. The RP2D/MTD will be established separately for Group 1 (recurrent disease) and Group 2 (maintenance setting) subjects. The interim analysis will include the establishment of RP2D/MTD and the estimate of ORR.

- The first interim of safety data analysis in Part 1 dose escalation will happen at the earlier of
  - When 15 subjects enrolled and completed DLT observation or
  - Completion of dose escalation of Group 1. Efficacy data will also be analyzed for subjects who have had at least one imaging evaluation after start of treatment or have dropped out before that.

Interim safety analyses during dose expansion will occur once 1) 5 subjects with recurrent disease have been enrolled and 2) after enrollment of 10 subjects with maintenance setting. The BLRM will estimate the RP2D/MTD using available data from dose escalation and dose expansion. Based on this revised RP2D/MTD estimate and reviewing all available safety data, the dose level for dose expansion may be revised.

In Part 2 dose expansion, the ORR will be evaluated after treating n=10 Group 2 subjects for at least 6 months. The futility will be assessed initially for N=10 and continuously afterwards using a Bayesian predictive probability design. Enrollment may be terminated if insufficient antitumor-activity is observed.

Arm 2

In dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a

BLRM design. The RP2D/MTD will be established separately for Group 1 (recurrent disease) and Group 2 (maintenance setting) subjects.

Interim safety analyses during dose expansion will occur once 1) 5 subjects with recurrent disease have been enrolled and 2) after enrollment of 10 subjects with maintenance setting. The BLRM will estimate the RP2D/MTD using available data from dose escalation and dose expansion. Based on this revised RP2D/MTD estimate and reviewing all available safety data, the dose level for dose expansion may be revised.

In Part 2 dose expansion, the ORR will be evaluated after treating n=10 Group 2 subjects for at least 6 months. The futility will be assessed initially for N=10 and continuously afterwards using a Bayesian predictive probability design. Enrollment may be terminated if insufficient antitumor-activity is observed.

10.4.2 Dose Level Review Team (DLRT)

Dose level review meetings (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/ Early Development Leader, Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager and Biostatistics representative. Additional members may be added as needed (eg, Biomarker Scientist, PK Scientist). A quorum, defined as > 50% of the participating investigators or their qualified designee [ie, sub-PI or research nurse or study coordinator possessing hard copy documentation (eg, email) of the PI's vote regarding the dose level review], must be in attendance for DLRM. The following DLRT members are responsible for dosing decisions: investigators, Amgen Medical Monitor, Early Development Leader, and Amgen Global Safety Officer. The DLRM will be rescheduled if a quorum is not reached.

The DLRT members are responsible for dosing decisions, which 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 or start of step-dosing. 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 by the team and can be considered in the DLRT's decisions. Data to be reviewed will be queried.

10.4.3 Primary Analysis

A primary analysis will be performed for each group separately when target enrollment in Part 1 and Part 2 is complete and each subject either completes 6 months on study or withdraws from the study.

10.4.4 Final Analysis

A final analysis for each group is planned after all subjects in each group have ended the study (parts 1 and 2).

10.5 Planned Methods of Analysis

10.5.1 General Considerations

The analyses described below will be reported separately for subjects enrolled to Arm 1 and for subjects enrolled to Arm 2. Unless otherwise specified, the analyses will be done using the Safety Analysis Set.

Descriptive statistics will be provided for selected demographics, safety, PK, PD, efficacy and biomarker data by dose, dose schedule, and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. ORR will be presented with 80% Clopper-Pearson exact CI using the RANO Evaluable Analysis Set. PFS will be summarized using Kaplan-Meier method. Graphical summaries of the data may also be presented.

10.5.2 Primary Endpoint(s)

Dose Limiting Toxicities (DLT)

The DLT endpoint will be analyzed using the DLT Evaluable Analysis Set. The probability of each TPI and of a DLT from the BLRM will be summarized by dose and group along with the estimated dose-toxicity curve. Subject incidence of DLT by dose level and group will be summarized.

Adverse Events

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.

Disease-Related Event (DREs)

Safety endpoints (eg, mortality and morbidity) that are study endpoints are reported on an eCRF. A negatively adjudicated safety endpoint will be reported to the investigator and treated by Amgen as appropriate. This could include no action, or a report on the eCRF as a Disease-Related event, an adverse event, or a serious adverse event.

Clinical Laboratory Tests

Clinical chemistry, hematology, and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference ranges will be flagged as high or low on the listings. Depending on the size and scope of changes in laboratory data, summaries of laboratory data over time and/or changes from baseline over time may be provided. Tables of maximum shifts from baseline for selected laboratory values may also be provided.

Vital Signs

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

Electrocardiograms

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

Subjects' maximum change from baseline in QTc 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.

10.5.3 Secondary Endpoint(s)

For all subjects in part 1 and part 2 listings will be produced indicating the time to progression, time to response, and duration of response.

Using the RANO Evaluable Analysis Set, an exact 80% CI will be estimated for the OR rate for all subjects in part 2 and those in part 1 treated at RP2D/MTD for each group. Among these subjects, the proportion of subjects that are progression free at 6 months and 12 months with corresponding exact 80% CI will be calculated. A Kaplan-Meier

curve may be presented for time to progression with estimates for rates and 80% CI at selected weeks.

Pharmacokinetic Analyses

The serum PK parameters of AMG 596 as monotherapy or in combination therapy with AMG 404 including, but not limited to, average C_{ss}, area under the concentration-time curve (AUC), clearance, volume of distribution, half-life ($t_{1/2}$), [redacted] and serum PK parameters of AMG 404 including, but not limited to, C_{max}, t_{max}, and AUC will be estimated using non-compartmental methods and summarized by dose level using means, standard deviations, medians, minimums, and maximums. [redacted] Summary statistics will be computed for each sampling time and parameter as appropriate.

10.5.4 Exploratory Endpoints

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Study Manager to the investigator.

The written informed consent form is to be prepared in the language(s) of the potential subject population.

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

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/ her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

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 informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

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

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(s), and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

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

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

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

Elements to include:

- Subject files containing completed eCRF, informed consent forms, and subject identification list.
- Study files containing the protocol with all amendments, 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 (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs 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, CRFs and other pertinent data) provided that subject confidentiality is respected.

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

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the 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 are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and agrees with the content.

Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the eCRF Standard Instructions and the eCRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit, [eg, week 4 and early termination]) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (see Section 7.1) 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

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICMJE, 2017). Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

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

Additional information on the current guidelines for publications can be found at the following location: http://www.icmje.org.

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.

13. REFERENCES

AMG 596 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

AMG 211 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

AMG 404 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.

Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Statistics in medicine. 1998: 17(10):1103-1120

Berghoff AS, Kiesel B, Widhalm G, Rajky O, Ricken G, Wöhrer A, Dieckmann K, Filipits M, Brandstetter A, Weller M, Kurscheid S, Hegi ME, Zielinski CC, Marosi C, Hainfellner JA, Preusser M, Wick W. Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. *Neuro Oncology*. 2015 Aug;17(8):1064-75.

Brown, C. E., D. Alizadeh, R. Starr, L. Weng, J. R. Wagner, A. Naranjo, J. R. Ostberg, M. S. Blanchard, J. Kilpatrick, J. Simpson, A. Kurien, S. J. Priceman, X. Wang, T. L. Harshbarger, M. D'Apuzzo, J. A. Ressler, M. C. Jensen, M. E. Barish, M. Chen, J. Portnow, S. J. Forman and B. Badie. "Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy." *New England Journal of Medicine* 2016;375(26): 2561-2569.

Burstein AH, Zhao Q, Ross J, Styren S, Landen JW, McCush F, et al. Safety and pharmacology of ponezumab (PF-0436035) after a single 10-minute intravenous infusion in subjects with mild to moderate Alzheimer disease. *Clin Neruropharmacol*. 2013;36(1):8-13.

Chen, J. R., H. Z. Xu, Y. Yao and Z. Y. Qin (2015). "Prognostic value of epidermal growth factor receptor amplification and EGFRvIII in glioblastoma: meta-analysis*." Acta Neurol Scand* 2015;132(5): 310-322.

Choi, B. D., C. T. Kuan, M. Cai, G. E. Archer, D. A. Mitchell, P. C. Gedeon, L. Sanchez-Perez, I. Pastan, D. D. Bigner and J. H. Sampson. "Systemic administration of a bispecific antibody targeting EGFRvIII successfully treats intracerebral glioma." *Proc Natl Acad Sci U S A* 2013;110(1): 270-275.

Cloughesy TF, Mochizuki AY, Orpilla JR, Hugo W, Lee AH, Davidson TB, Wang AC, Ellingson BM, Rytlewski JA, Sanders CM, Kawaguchi ES, Du L, Li G, Yong WH Gaffey SC, Cohen AL, Mellinghoff IK, Lee EQ, Reardon DA, O'Brien BJ, Butowski NA, Nghiemphu PL, Clarke JL, Arrillaga-Romany IC, Colman H, Kaley TJ, de Groot JF, Liau LM, Wen PY, Prins RM. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. *Nat Med*. 2019 Mar;25(3):477-486.

De Vries, E., Heinemann, V., Fiedler, W.M. et al, Phase I study of AMG 211/MEDI565 administered as continuous intravenous infusion for relapsed/refractory gastrointestinal (GI) adenocarcinoma. J Clin Oncol 2015;33, (suppl; abstr TPS3097).

Gedeon, P. C., B. D. Choi, T. R. Hodges, D. A. Mitchell, D. D. Bigner and J. H. Sampson. "An EGFRvIII-targeted bispecific T-cell engager overcomes limitations of the standard of care for glioblastoma." *Expert Rev Clin Pharmacol* 2013;6(4): 375-386.

Klinger M, Zugmaier G, Naegele V, Goebeler M, Brandl C, Bargou RC, and Kufer P, "Pathogenesis-Based Development of Potential Mitigation Strategies for Blinatumomab-Associated Neurologic Events (NEs)", Blood 2016 (ASH abstract).

Kischel, R., A. Sternjak, J. Wahl, I. Herrmann, O. Thomas, M. Balazs, M. Voelkel, S. Stienen, B. Rattel, P. Kufer, M. Friedrich and M. Muenz. "Preclinical characterization of an EGFRvIII/CD3 specific BiTE® antibody construct for the treatment of glioblastoma multiforme." *European Journal of Cancer* 2016;69: S96.

Kufer P, Kischel R, Zugmaier G, Lichtenegger FS, Kohnke T, Vick B, Jeremias I, Metzeler KH, Altmann T, Schneider S, Fiegl M, Spiekermann K, Bauerle PA, Hiddemann W, Riethmüller G, Subklewe M. Blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: reversing a T-cell-induced immune escape mechanism. *Leukemia* (2016) 30:484–91.

Lee, D. W., R. Gardner, D. L. Porter, C. U. Louis, N. Ahmed, M. Jensen, S. A. Grupp and C. L. Mackall. "Current concepts in the diagnosis and management of cytokine release syndrome." *Blood* 2014;124(2): 188-195.

Lee, Bioinformatics. 2008 Nov 1;24(21):2542-3.

Louis, D. N., A. Perry, G. Reifenberger, A. von Deimling, D. Figarella-Branger, W. K. Cavenee, H. Ohgaki, O. D. Wiestler, P. Kleihues and D. W. Ellison. "The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary." *Acta Neuropathol* 2016;131(6): 803-820.

Mellinghoff, I. K., M. Y. Wang, I. Vivanco, D. A. Haas-Kogan, S. Zhu, E. Q. Dia, K. V. Lu, K. Yoshimoto, J. H. Huang, D. J. Chute, B. L. Riggs, S. Horvath, L. M. Liau, W. K. Cavenee, P. N. Rao, R. Beroukhim, T. C. Peck, J. C. Lee, W. R. Sellers, D. Stokoe, M. Prados, T. F. Cloughesy, C. L. Sawyers and P. S. Mischel. "Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors." *N Engl J Med* 2005;353(19): 2012-2024.

Mendelsohn, J. and J. Baselga. "Epidermal growth factor receptor targeting in cancer." *Semin Oncol* 2006;33(4): 369-385.

Mehta, M., Wen, P., Nishikawa, R., Reardon, D., & Peters, K. Critical review of the addition of tumor treating fields (TTFields) to the existing standard of care for newly diagnosed glioblastoma patients. *Crit Rev Oncol Hematol, 2017;111*, 60-65.

Neuenschwander, B., M. Branson and T. Gsponer. "Critical aspects of the Bayesian approach to phase I cancer trials." *Stat Med* 2008;27(13): 2420-2439.

Okada, H., M. Weller, R. Huang, G. Finocchiaro, M. R. Gilbert, W. Wick, B. M. Ellingson, N. Hashimoto, I. F. Pollack, A. A. Brandes, E. Franceschi, C. Herold-Mende, L. Nayak, A. Panigrahy, W. B. Pope, R. Prins, J. H. Sampson, P. Y. Wen and D. A. Reardon. "Immunotherapy response assessment in neuro-oncology: a report of the RANO working group." *Lancet Oncol* 2015;16(15): e534-542.

Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., McFadden, E. T., & Carbone, P. P. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol, 1982;5*(6), 649-655.

Omuro, A. and L. M. DeAngelis. "Glioblastoma and other malignant gliomas: a clinical review." *JAMA* 2013;310(17): 1842-1850.

Omuro, A. , Vlahovic, G., Lim,M., Sahebjam,S., Baehring, J.,, Cloughesy, T.,, Voloschin, A., Ramkissoon, S.H., Ligon, K.L.,Latek,R. ,Zwirtes, R. Strauss,L., Paliwal, P., Harbison, C.T., Reardon, D.A.,Sampson, J.H.,Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. *Neuro Oncol*. 2018;20(5):674-686

Ostrom Q T, L. Bauchet, F. G. Davis, I. Deltour, J. L. Fisher, C. E. Langer, M. Pekmezci, J. A. Schwartzbaum, M. C. Turner, K. M. Walsh, M. R. Wrensch and J. S. Barnholtz-Sloan. "The epidemiology of glioma in adults: a "state of the science" review." *Neuro Oncol* 2014;16(7): 896-913.

Osada T, Patel SP, Hammond SA, Osada K, Morse MA, Lyerly HK.CEA/CD3-bispecific T cell-engaging (BiTE) antibody-mediated T lymphocyte cytotoxicity maximized by inhibition of both PD1 and PD-L1. *Cancer Immunol Immunother*. (2015) 64:677–88.

Peter F. Thall, Richard M. Simon, and Elihu H. Estey, Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes, Statistics in Medicine, vol 14, 357-379 (1995).

Platten M, Bunse L, Wick W and Bunse T. "Concepts in glioma immunotherapy." *Cancer Immunol Immunother* 2016 Jul 26.

Reardon, D.A., Omuro, A., Brandes, A.A., Rieger, J., Wick,A., Sepulveda,J., Phuphanich,S., de Souza, P., Ahluwalia, M.S., Lim,M., Vlahovic, G., Sampson, J., et al., 2017a. OS10.3: randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. *Neuro Oncol.* 2017 V19 Page iii21

Reardon, D.A, Kim, T.,Frenel, J.S.,Santoro, A., Lopez, J., Subramaniam, D.S., Siu, L.L.,Rodon,J., Tamura, K.,Saraf, S., Morosky, A., Stein, K., Soria, J.C., ATIM-35. Results of the phase Ib Keynote-028 multi-cohort trial of pembrolizumab monotherapy in patients with recurrent PD-L1 positive Glioblastoma Multiforme (GBM), *Neuro Oncology*. 2016 V18, P25-26

Reardon, D. A., Nayak, L., Peters, K.B., Clarke, J.L., Jordan, J. T., Groot, J. F., Nghiemphe, P. L., Kaley, T. J., Colman,H., Gaffey, S.C., Caruso, V., Debruyne, M. B., Bahavsar, C., Molinaro, A. M., Smith, T., Severgnini, M., Wen, P. Y., Phase II study of pembrolizumab or pembrolizumab plus bevacizumab for recurrent glioblastoma (rGBM) patients. *Journal of Clinical* Oncology, 2018, 36, no. 15_suppl (May 20 2018) 2006-2006

Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, López-Janeiro A, Porciuncula A, Idoate MA, Inogés S, de Andrea C, López-Diaz de Cerio A, Tejada S, Berraondo P, Villarroel-Espindola F, Choi J, Gúrpide A, Giraldez M, Goicoechea I Gallego Perez-Larraya J, Sanmamed MF, Perez-Gracia JL, Melero I. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma.*Nat Med*. 2019 Mar;25(3):470-476

Stewart, L.A. "Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials." *Lancet* 2002;359(9311): 1011-1018.

Tabrizi M, Bornstein GG, Suria H. Biodistribution mechanisms of therapeutic monoclonal antibodies in health and disease. *AAPS J.* 2010;12(1):33-43

Wang, X.,Guo, G.,Guan, H.,Yu, Y.,Lu, J., and Yu, J. Challenges and potential of PD-1/PD-L1 checkpoint blockade immunotherapy for glioblastoma.*J Exp Clin Cancer Res.* 2019;38(1) 87. doi: 10.1186/s13046-019-1085-3.

Wen PY, Macdonald DR, Reardon DA, Cloughesy, TF, Sorensen AG, Galanis E. Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain, M. C., Stupp, R., Lamborn, K. R., Vogelbaum, M. A., van den Bent, M. J.

Wong, A. J., J. M. Ruppert, S. H. Bigner, C. H. Grzeschik, P. A. Humphrey, D. S. Bigner and B. Vogelstein. "Structural alterations of the epidermal growth factor receptor gene in human gliomas." *Proc Natl Acad Sci U S A* 1992;89(7): 2965-2969.

Zhao J, Chen AX, Gartrell RD, Silverman AM, Aparicio L, Chu T, Bordbar D, Shan D, Samanamud J, Mahajan A, Filip I, Orenbuch R, Goetz M, Yamaguchi JT, Cloney M, Horbinski C, Lukas RV, Raizer J, Rae AI, Yuan J, Canoll P, Bruce JN, Saenger YM, Sims P, Iwamoto FM, Sonabend AM, Rabadan R “Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. *Nat Med*. 2019; 25(3):462-469.

14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE V 4.0) is available at the following location:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40

If the Amgen standard scoring system is used, insert the following table:

Grade	Amgen Standard Adverse Event Grading Scale
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

It is recommended that teams use the same version of CTCAE throughout a program instead of migrating to a newer version in order to avoid the potential for introducing discrepancies between studies within a program.]

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 6.3 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event as defined in Section 9.1.3.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.3.3, Section 6.3.4, Section 6.3.5 and Section 6.3.6. or who experience AST or ALT elevations > 3 x ULN or 2-fold increase above baseline values for subjects with evaluated values before drug are to undergo a period of “close observation” until

abnormalities return to normal or to the subject's baseline levels. Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve
- Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.
- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:
  - Complete blood count (CBC) with differential to assess for eosinophilia
  - Serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Serum acetaminophen (paracetamol) levels
  - A more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Viral serologies
  - Creatine phosphokinase (CPK), haptoglobin, Lactate dehydrogenase (LDH), and peripheral blood smear
  - Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

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

Appendix B. Electronic Serious Adverse Event Contingency Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

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

   Age at event onset, Sex, and Race – Enter the subject's demographic information

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

If you are submitting follow-up information to a previous report, provide the serious 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 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 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 the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and 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 Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. 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 criterion.

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

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

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

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

4. **Hospitalization**

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

Completion Instructions - Electronic Adverse Event Contingency Report 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, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

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

5. **IP Administration including Lot # and Serial # when known / available.**

   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. **Concomitant Medications**

   Indicate if there are any medications.

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

   Co-suspect – Indicate if the medication is 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.

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).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

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 # 20160132 AMG 596	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year____

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

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 08 Other medically important serious event

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

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

AMGEN Study # 20160132 AMG 596	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

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

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

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

Date Day Month Year	Test / Unit											
	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

AMGEN Study # 20160132 AMG 596	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

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

Signature of Investigator or Designee -	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: 20160132

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: 20160132

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 Response Assessment In Neuro-Oncology (RANO)

The RANO criteria are extentions to the Macdonald criteria that incorporate T2/ FLAIR images to better capture lesion response (Wen et al, 2010). Here, the RANO criteria are further modified to capture pseudoprogression and delayed responses which may be observed in response to immunotherapies (Okada et al, 2015).

Patients require at least 1 bi-dimensionally measurable contrast-enhancing lesion that can be accurately assessed at baseline by magnetic resonance imaging (MRI) to be included in this a study.

Definitions:

- Measurable lesions contrast-enhancing lesions that can accurately be measured bidimensionally with ≥ 10mm longest diameter and ≥ 10mm perpendicular diameter and noted on more than one imaging slice.
- Non-measurable lesions – all other lesions, including small lesions, ie, bone lesions, leptomeningeal disease and cystic lesions that are not confirmed and followed by imaging techniques.

Documentation of index and non-index lesions:

- Index Lesions
  - All measureable lesions (up to 5) should be identified as index lesions, measured and recorded during screening.
  - Enhancing lesions should be selected based on size (largest cross-sectional area) and suitability for accurate repeat measure (clearly defined borders)
  - The sum of bidimensional products (total cross-sectional area of measurable lesions) for all enhancing measurable lesions at screening will be calculated and reported as the baseline disease burden.
  - Baseline disease burden will be the reference used to characterize radiographic objective tumor response.
  - Baseline or nadir, whichever is smaller, is used to calculate PD.
- Non-Index Lesions
  - All other lesions (or sites of disease) should be identified and recorded as non-index lesions during screening.
  - Measurable lesions located in previously irradiated sites that have not since shown documented progression are non-index lesions.
  - Incidental new lesions will be recorded and tracked as non-index lesions.
  - Measurement of non-index lesions is not required, but absence or presence and qualitative changes (unequivocal response, stable, unequivocal progression) should be recorded throughout the study.

Table 21. Measurement Summary

Imaging modality	**MRI**
Sequences for this protocol	- Axial Pre Contrast (2D) T1 - Axial T2/FLAIR - Axial T2 - Axial Post Contrast (2D) T1 - Axial DWI (at selected sites) - Sagittal Post Contrast (3D) T1 (at selected sites)
Measurement technique	Bidimensional; sum of products of perpendicular diameters
Imaging intervals	Screening, every 10-12 weeks, SFUP, LTFU
Measurable lesions	Contrast-enhancing lesions with ≥ 10mm longest diameter and ≥ 10mm perpendicular diameter
Measurable disease	One to five index lesions

Table 22. Response Assessment

All % changes are calculated as change from baseline burden, except PD which is baseline or nadir.	
Complete response (CR)	• Disappearance of all enhancing disease • no new lesions • stable or improved T2/FLAIR • no more than physiological steroids • clinically stable or improved • Disappearance confirmed with follow-up scan after ≥ 4 weeks
Partial response (PR)	• ≥ 50% decrease in the sum of perpendicular diameters of enhancing disease from baseline • stable or improved T2/FLAIR • stable or decreased steroid dose • clinically stable or improved • Decrease confirmed with follow-up scan after ≥ 4 weeks
Stable disease (SD)	• Changes do not qualify for CR, PR or PD • stable or improved T2/FLAIR • stable or decreased steroid dose • clinically stable or improved
Progressive disease (PD)	Any of the below • ≥ 25% increase in the sum of perpendicular diameters of enhancing disease from the lesser of baseline or nadir • or substantially worsened T2/FLAIR • or unequivocal progression in new lesions • or substantial clinical decline • Increase confirmed with follow-up scan ≥ 4 weeks after initial observation.

Reponses (CR and PR) are dated at time of confirmation scan.

Progression (PD) is backdated to initial observation, if confirmed.

Patients with a neurological decline attributable to their underlying tumor requiring discontinuation of treatment without objective evidence of measurable radiographic disease progression at that time should be classifies as having “clinical deterioration.” Every effort should be made to document the radiographic progression even after discontinuation of treatment.

Appendix E. Grading and Management of Cytokine Release Syndrome (CRS)

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of Dosing
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever). Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier.	N/A
2	Symptoms require and respond to moderate intervention Oxygen requirement < 40%, OR Hypotension responsive to fluids or low dose of one vasopressor, OR Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Administer: Symptomatic treatment (eg, paracetamol/ acetaminophen for fever) Supplemental oxygen when oxygen saturation is < 90% on room air Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg > 120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below.	Immediately interrupt dosing until event resolves to CRS grade ≤ 1 but for no less than 72 hours. Permanently discontinue AMG 596 and AMG 404 if there is no improvement to CRS ≤ grade 1 within 7 days.

Footnotes defined on the next page of the table

Appendix E. Grading and Management of Cytokine Release Syndrome (CRS) (Continue)

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of Dosing
3	Symptoms require and respond to aggressive Intervention Oxygen requirement ≥ 40%, OR Hypotension requiring high dose[b] or multiple vasopressors, OR Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise. Investigators may also consider use of Tocilizumab as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose.	Immediately interrupt dosing until event resolves to CRS grade ≤ 1 but for no less than 72 hours. Permanently discontinue AMG 596 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days.
4	Life-threatening symptoms requirement for ventilator support OR Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, Tocilizumab can be considered administered at a dose of 4-8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	Immediately stop the infusion and permanently discontinue AMG 596 and AMG 404 therapy.

CRS: Cytokine release syndrome; CTCAE: Common terminology criteria for adverse events; IV: Intravenous
[a] Revised grading system for cytokine release syndrome (Lee et al, 2014)
[b] High dose vasopressors (all doses are required for ≥ 3 hours): Norepinephrine monotherapy ≥ 20 µg/min; Dopamine monotherapy ≥ 10 µg/kg/min, Phenylephrine monotherapy ≥ 200 µg/min, Epinephrine monotherapy ≥ 10 µg/min; If on Vasopressin, Vasopressin + Norepinephrine equivalent of ≥ 10 µg/min; If on combination vasopressors (not Vasopressin), Norepinephrine equivalent of ≥ 20 µg/min

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

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

Reference: (Oken et al., 1982)

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Pneumonitis	Grade 2 (symptomatic, involves more than one lobe of the lung of 25-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider additional immunosuppressive agent (eg, infliximab, mycophenolate, cyclophosphamide) if refractory to corticosteroids.	Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 (severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, limiting self-care ADL, oxygen indicated)	Permanently discontinue		
	Grade 4 (life-threatening respiratory compromise, urgent intervention indicated [intubation])			

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Colitis/Diarrhea	Grade 2 (increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared with baseline)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider infliximab if symptoms refractory to corticosteroids within 2-3 days.	Monitor subjects for signs and symptoms of enterocolitis (eg, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (eg, peritoneal signs and ileus). For subjects with grade ≥2 diarrhea suspecting colitis, consider GI consultation and endoscopy to rule out colitis.
	Grade 3 (increase of 7 or more stools per day over baseline, incontinence; hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL)			
	Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue		

Page 2 of 8

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hepatitis	Grade 2 (asymptomatic, AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN [for patients with values < ULN at baseline])	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor with liver function tests more frequently until returned to baseline or stable.
	Grade 3 (symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis [AST or ALT 5-20 x ULN and/or total bilirubin 3-10 x ULN])	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	
	Grade 4 (decompensated liver function eg, ascites, coagulopathy, encephalopathy, coma [AST or ALT > 20 x ULN and/or total bilirubin > 10 x ULN])		Administer corticosteroids at an initial dose of 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider mycophenolate mofetil if refractory to corticosteroids or no improvement after 3 days.	

Page 3 of 8

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Hypophysitis	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Administer corticosteroids at an initial dose of 1 mg/kg/d prednisone (or equivalent) followed by taper. In addition, initiate hormonal replacement therapy as clinically indicated.	Monitor for signs and symptoms of hypophysitis. Consider endocrine consultation.
Adrenal Insufficiency	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and ACTH stimulation testing will be needed]). Taper stress-dose corticosteroids down to maintenance doses (prednisone 5 to 10 mg daily) over 1-2 weeks after discharge.	Monitor for signs and symptoms of adrenal insufficiency. Consider endocrine consultation.
Hypothyroidism	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate thyroid hormone supplementation.	Monitor subjects for signs and symptoms of hypothyroidism. Consider endocrine consultation.
Hyperthyroidism	Grade 3 or 4 (severe symptoms, medically significant or life-threatening consequences, unable to perform ADL)	Withhold	Initiate β-Blocker (eg, atenolol, propranolol) for symptomatic relief. For severe symptoms or concern for thyroid storm, initiate prednisone 1-2 mg/kg/d (or equivalent) tapered over 1-2 weeks. Consider use of SSKI or thionamide (methimazole or PTU).	Monitor subjects for signs and symptoms of hyperthyroidism. Consider endocrine consultation.

Page 4 of 8

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Diabetes Mellitus	Grade 3 hyperglycemia (> 250 to 500 mg/dL [> 13.9 to 27.8 mmol/L])	Withhold	Initiate insulin therapy.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Consider endocrine consultation.
	Grade 4 hyperglycemia (> 500 mg/dL [> 27.8 mmol/L])			
Nephritis and Renal Dysfunction	Grade 2 (serum creatinine >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN)	Withhold	Administer corticosteroids at an initial dose of 0.5 to 1 mg/kg/d prednisone (or equivalent) followed by taper. If worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/d prednisone (or equivalent).	Monitor changes in renal function. Evaluate for other causes of renal dysfunction (eg, recent IV contrast, medications, fluid status, etc)
	Grade 3 (serum creatinine >3.0 x baseline; >3.0 - 6.0 x ULN)	Permanently discontinue	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	
	Grade 4 (serum creatinine > 6 x ULN; dialysis indicated)			

Page 5 of 8

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids as indicated.	Monitor subjects for suspected severe skin reactions and exclude other causes (eg, infection, an effect of another drug, a skin condition linked to another systemic disease, etc). For signs or symptoms of SJS or TEN, withhold study drug and refer the patient for specialized care for assessment and treatment.
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue		
Encephalitis	Grade 2 (moderate symptoms, some interference with ADL)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper. Consider empirical antiviral (IV acyclovir) and antibacterial therapy until CSF results obtained and negative for aseptic meningitis.	Monitor subjects for neurologic symptoms and exclude other etiologies (eg, infectious). Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.
	Grade 3 or 4 (severe symptoms, limiting self-care and aids warranted)	Permanently discontinue		

Page 6 of 8

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Myocarditis	Grade 1 (abnormal cardiac biomarker testing, including abnormal ECG)	Withhold	Administer corticosteroids at an initial dose of 1 to 2 mg/kg/d prednisone (or equivalent) followed by taper.	Monitor patients with cardiovascular symptoms. Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2 (abnormal screening tests with mild symptoms)			
	Grade 3 (moderately abnormal testing or symptoms with mild activity)	Permanently discontinue		
	Grade 4 (moderate to severe decompensation, IV medication or intervention required, life-threatening conditions)			
All Other Immune-Related Adverse Reactions	Grade 3 adverse reaction involving a major organ	Withhold	Based on type and severity of adverse reaction, administer corticosteroids. Refer to ASCO Clinical Practice Guidelines for additional recommendations.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Life-threatening or Grade 4 adverse reaction involving a major organ	Permanently discontinue		

Page 7 of 8

Footnotes defined on last page of this table

Appendix G. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated With AMG 404*

Immune-Related Adverse Reactions	Severity (CTCAE Grade Version 4.0 or Specific Conditions)	AMG 404 Dose Modification	Management with Corticosteroids and/or Other Therapies	Monitor & Follow-up
Recurrent or Persistent Immune-Related Adverse Reactions	Recurrence of same Grade 3 or Grade 4 adverse reaction	Permanently discontinue	Based on type and severity of adverse reaction, administer corticosteroids. Additional immunosuppressive treatment may be required.	Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Requirement for ≥ 10 mg/day prednisone (or equivalent) for more than 12 weeks			
	Persistent grade 2 or 3 adverse reactions lasting 12 weeks or longer after last dose (ie, does not resolve to grade 0 or 1 within 12 weeks)			

General considerations:

- Corticosteroid taper should be initiated upon improvement of signs/symptoms and/or laboratory values to Grade 1 or less. Continue corticosteroid taper over the course of at least 4 to 6 weeks.
- If AMG 404 has been withheld, treatment with AMG 404 may be resumed after adverse event (or associated signs/symptoms/laboratory parameters) has been reduced to Grade 1 or less and corticosteroid has been tapered to prednisone < 10 mg (or equivalent).
- For severe and life-threatening immune-related adverse reactions, IV corticosteroids should be initiated first followed by oral corticosteroids. Other immunosuppressive treatment should be initiated if the event cannot be controlled by corticosteroids.

Page 8 of 8

** Recommendations adapted from the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines for the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy (JCO 2018)*

Appendix H. Management of Infusion Related Reactions With AMG 404

Severity (CTCAE Grade Version 4.0)	AMG 404 Dose Modification	Management	Premedication at Subsequent Dosing
Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)	Interrupt or slow the rate of the infusion.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines.	None
Grade 2 (therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours)	Interrupt or slow the rate of the infusion. For subjects who develop grade 2 infusion-related reaction despite adequate premedication, permanently discontinue AMG 404.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of AMG 404 with: • Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).
Grade 3 (prolonged [eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae) OR Grade 4 (life-threatening consequences; urgent intervention indicated)	Permanently discontinue study drug.	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable. • Hospitalization may be indicated. • Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids, and epinephrine. In cases of anaphylaxis, epinephrine should be used immediately.	No subsequent dosing

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

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See [Section 9.2.3.1.1.1 / Section 12.8] for the list of disease-related events. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  • An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
  • An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Amendment 5

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 as a Monotherapy and in Combination With AMG 404 in Subjects With Glioblastoma or Malignant Glioma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Amgen Protocol Number 20160132

IND Number 134352

EudraCT number 2017-001658-32

Amendment Date: 29 July 2019

Rationale:

The combination of AMG 596 with the checkpoint inhibitor AMG 404 is seen as a promising approach in the treatment of glioblastomas and can now be supported by preclinical data and available initial safety data for AMG 596 and for AMG 404. Also, a first objective response has been observed with AMG 596 monotherapy in a subject with recurrent glioblastoma and there is a high interest of study investigators to enroll subjects in the study. In order to extent the opportunity with the potential for an even more effective combination therapy we are amending the ongoing FIH study protocol. Protocol Amendment 5 includes adding combination therapy of AMG 596 and AMG 404, and also to start enrollment of Group 2 subjects (newly diagnosed glioblastoma) after observation of a first partial response in separate cohorts.

Revisions to Protocol Amendment 5 include:

- Adding combination therapy of AMG 596 and AMG 404 in protocol synopsis and main protocol text.
- Add background information, mechanism of action of AMG 404, dosing rational and risk evaluation for AMG 596 in combination with AMG 404.
- Add terminology of Arm 1 and Arm 2. Arm 1 refers to AMG 596 monotherapy. Arm 2 refers to AMG 596 and AMG 404 combination therapy.
- Allow newly diagnosed glioblastoma to enroll at current highest safe dose from Group 1 subjects.
- Update the treatment schema to reflect the addition of AMG 596 and AMG 404 combination therapy in both recurrent glioblastoma (group 1) and in maintenance of newly diagnosed Glioblastoma after standard of care therapy.
- Update sample size in both dose escalation phase and dose expansion phase in monotherapy and combination therapy in Group 1 and Group 2.

- Add appendix G for Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated with AMG 404*
- Add appendix H for Management of infusion-related reactions with AMG 404

- Update ECG triplicate collection upon AMG 404 infusion.
- Update exclusion criteria to add AMG 404 exclusion criteria
- Added language for prophylactic use of corticosteroid prior to C1D1 of treatment

In addition, clarifications and corrections of inconsistencies, and administrative and typographical changes were made throughout the protocol.

Below are Description of changes:

Section	Amended text
Global, Key Sponsor Contacts	~~Replace~~ [redacted] ~~Clinical Research Study Manager~~ ~~Phone~~ ~~Email:~~ [redacted] With [redacted]**, PhD** **Clinical Research Study Manager** **Phone:** [redacted] **Email:** [redacted]
Global	The version is updated to Amendment **5** and the date is updated to 29 July 2019.
Investigators agreement	Replace: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 in Subjects with Glioblastoma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII) With Phase 1[redacted]Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 **as Monotherapy and in Combination with AMG 404** in Subjects with Glioblastoma **or Malignant Glioma** Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)
Investigators agreement	Replace 11 March 2019 With 29 July 2019

Section	Amended text
P3, Protocol Synopsis, Primary Objective	Replace Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and afterwards in the maintenance treatment phase of newly diagnosed glioblastoma (maintenance setting) (Group 2) With Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion **in monotherapy (Arm 1) and in combination with AMG 404 (anti-programmed cell death-1 (PD-1) antibody (Arm 2)** in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and in the maintenance treatment phase of newly diagnosed glioblastoma (maintenance setting, Group 2).
P3, Protocol Synopsis, Secondary Objective	**Replace** Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion With Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion **either in monotherapy or in combination with AMG 404**
P3, Protocol Synopsis, Secondary Objective	Add **Evaluate the pharmacokinetics (PK) of AMG 404 in serum when administered by short term infusion in combination with AMG 596**
P3, Protocol Synopsis, Secondary Objective	Replace Evaluate the clinical benefit of AMG 596 as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent and in the maintenance setting With Evaluate the clinical benefit of AMG 596 or **AMG 596 in combination with AMG 404** as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO) in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent and in the maintenance setting

Section	Amended text
P3, Protocol Synopsis, Secondary Objective	Replace: Evaluate progression free survival (PFS) at 6 and 12 months after initiation of treatment With: Evaluate progression free survival (PFS) at 6 and 12 months after initiation of treatment **for any Part, Arm and Group of the study**
P3, Protocol Synopsis, Exploratory Objective	Replace Evaluate the pharmacokinetics (PK) of AMG 596 in cerebrospinal fluid (CSF) With Evaluate the pharmacokinetics (PK) of AMG 596 **and AMG 404** in cerebrospinal fluid (CSF)
P3, Protocol Synopsis, Exploratory Objective	[redacted]
P3, Protocol Synopsis, Exploratory Objective	

Section	Amended text
P3, Protocol Synopsis, Hypotheses	Replace AMG 596 is safe and well tolerated in at least one dose level when administered in subjects with EGFRvIII-positive glioblastoma, or malignant glioma in the recurrent (Group 1) and ~~thereafter~~ in the maintenance setting (Group 2) With AMG 596 **monotherapy and in combination with AMG 404 are** safe and well tolerated in at least one dose level when administered in subjects with EGFRvIII-positive glioblastoma, or malignant glioma in the recurrent (Group 1) and in the maintenance setting (Group 2) Replace AMG 596 can induce objective tumor shrinkage and/or overcome lack of response to SoC in subjects with EGFRvIII-positive glioblastoma or malignant glioma in either recurrent or in the maintenance setting at a tolerable dose With AMG 596 **monotherapy and/or AMG 596 in combination with AMG 404** can induce objective tumor shrinkage and/or overcome lack of response to SoC in subjects with EGFRvIII-positive glioblastoma or malignant glioma in either recurrent or in the maintenance setting at a tolerable dose
P4, Protocol Synopsis, Secondary Endpoint	Add **PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (C_{max}), time to achieve C_{max} (t_{max}), and AUC**
P4, Protocol Synopsis, Secondary Endpoint	Add **PK parameters for AMG 596 dosed in combination with AMG 404 including, but not limited to, average steady-state concentration (C_{ss}), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life (t1/2) for serum AMG 596**

Section	Amended text
P4, Protocol Synopsis, Secondary Endpoint	Replace Objective response (OR) as per modified RANO, time to response, response duration and time to progression (TTP); progression free survival (PFS) at 6 and 12 months after treatment initiation With Objective response (OR) as per modified RANO, time to response, response duration and time to progression (TTP); progression free survival (PFS) at 6 and 12 months after treatment initiation **with AMG 596 monotherapy or AMG 596 in combination with AMG 404**
P4, Protocol Synopsis, Exploratory Endpoints	[redacted]
P4, Protocol Synopsis, Exploratory Endpoints	
P4, Protocol Synopsis, Study Design	Replace This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma. The study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). This study will enroll 2 groups of subjects according to disease stage, recurrent disease (Group 1) and maintenance treatment after SoC in newly diagnosed disease (Group 2). With This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma **exploring AMG 596 monotherapy (Arm 1) and in combination with AMG 404 (Arm 2). Both Arm 1 and Arm 2** consist of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). **Both Arm 1 and Arm 2** will enroll 2 groups of subjects according to disease stage, recurrent disease (Group 1) and maintenance treatment after SoC in newly diagnosed disease (Group 2).

Section	Amended text
P4, Protocol Synopsis, Study Design	Replace The purpose of dose escalation is to make a preliminary estimate of the Recommended Phase 2 Dose (RP2D)/ Maximum Tolerated Dose (MTD) of AMG 596. With *Part 1, Dose Escalation:* The purpose of dose escalation is to make a preliminary estimate of the Recommended Phase 2 Dose (RP2D)/ Maximum Tolerated Dose (MTD) of **AMG 596 monotherapy and in combination with AMG 404.**
P4, Protocol Synopsis, Study Design	Replace Treatment is divided into 2 periods: (1) DLT period 1 for [redacted] of AMG 596 infusion and (2) DLT period 2 for [redacted] of infusion. With Treatment is divided into 2 periods: (1) DLT period 1 for [redacted] of AMG 596 infusion and (2) DLT period 2 for [redacted] of infusion **(applies for both Arms)**.
P4, Protocol Synopsis, Study Design	Add **resulting in the utilization of**
P4, Protocol Synopsis, Study Design	Replace Further pre-specified nominal doses for use in the dose escalation are [redacted], [redacted] µg/day. With Further pre-specified nominal **AMG 596** doses for **potential** use in **any** dose escalation **Arms** are [redacted] µg/day.

Section	Amended text
P4, Protocol Synopsis, Study Design, (beginning of page 4)	Replace The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and subsequently in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2). In the multiple subject cohorts a safety observation window of at least 72 hours must apply between start of subjects 1, 2 and 3 of each dose escalation cohort. Intra-subject dose escalation will be allowed to higher dose levels in subsequent treatment cycles once a higher dose has been deemed safe by the DLRT. Subjects who do not proceed to a higher dose may continue at the original dose. With The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and **separately** in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2) and **separately for AMG 596 monotherapy and in combination with AMG 404**. **If the same AMG 596 doses are to be explored in monotherapy and in combination, the monotherapy cohort must be completed before enrollment in the combination cohort.** In the multiple subject cohorts, a safety observation window of at least 72 hours must apply between start of subjects 1, 2 and 3 of each dose escalation cohort. Intra-subject dose escalation will be allowed to higher **AMG 596** dose levels in subsequent treatment cycles once a higher dose has been deemed safe by the DLRT. Subjects who do not proceed to a higher dose may continue at the original dose.
P4, Protocol Synopsis, Study Design	Delete ~~Dose Escalation in Group 1 will proceed using 2 phases~~
P5, Protocol Synopsis, Group 1, Recurrent Disease,	Replace *Dose Escalation phase 1in single subject cohorts* With *Dose Escalation in single subject cohorts*
P5, Protocol Synopsis, Group 1, Recurrent Disease,	Add **Combination of AMG 596 and AMG 404: The starting dose of AMG 596 is [redacted] ug/day administered in [redacted] cycles and the defined AMG 404 dose is [redacted] mg every 4 weeks.**

Section	Amended text
P5, Protocol Synopsis, Group 1, Recurrent Disease	Delete ~~The DLT period is 28 days; DLT period 1 is from [redacted] of AMG 596 infusion, and DLT period 2 is from [redacted] of infusion (including cycle 2).~~
P5, Protocol Synopsis, Group 1, Recurrent Disease	Replace The cohort size will be increased to N=2-4 subjects (ie, Start of Dose Escalation Phase 2, multiple subject cohorts) after observation of With The cohort size will be increased to N=2-4 subjects (ie, Start of multiple subject cohorts) after observation of
P5, Protocol Synopsis, Dose Escalation phase 2	Replace *Dose Escalation Phase 2, multiple subject cohorts* With *Dose Escalation **in** multiple subject cohorts*
P5, Protocol Synopsis, Dose Escalation phase 2	Replace All subjects receive [redacted] treatment break until treatment discontinuation criteria apply. With All subjects receive **AMG 596** in [redacted] infusion cycles until treatment discontinuation criteria apply
P5, Protocol Synopsis, Dose Escalation in multiple subject cohorts	Delete ~~In the first cycle, DLT period 1 is from [redacted] of AMG 596 infusion and DLT period 2 is from [redacted] infusion.~~

Section	Amended text
P5 Protocol Synopsis, Group 1, Recurrent Disease	Replace The maximum total sample size of N=30 DLT evaluable subjects (including single subject cohorts) is reached With The maximum total sample size of N=**45** DLT evaluable subjects (including single subject cohorts) is reached **for AMG 596 monotherapy and N=30 DLT evaluable subjects for AMG 596 in combination with AMG 404**
P6, Protocol Synopsis, Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease	Replace A first cohort will start after RP2D/MTD has been established in Group 1 subjects with recurrent EGFRvIII-positive glioblastoma or malignant glioma. The starting dose in Group 2 will be decided by the DLRT and will be the MTD of Group 1, or will be no higher than a 2-fold increase of the Group 1 RP2D if no MTD was reached and no DLT was observed at the highest dose administered in Group 1 dose escalation. With A first cohort will start **after observation of a first objective anti-tumor response in Group 1 subjects with recurrent EGFRvIII-positive glioblastoma or malignant glioma.** The starting dose of **AMG 596 monotherapy** in Group 2 **will be decided by DLRT and will be the highest dose deemed safe of Group 1.**
P6, Protocol Synopsis, Group 2,	Replace The BLRM will be used to guide dose level selection. The cohort size will be ~~N=4-6~~ subjects. With The BLRM will be used to guide dose level selection. The cohort size will be **N=2-4** subjects.
P6, Protocol Synopsis, Group 2,	Replace The maximum sample size of N=12 DLT evaluable subjects is reached With The maximum sample size of **N=15** DLT evaluable subjects is reached for AMG 596 monotherapy or **N=20 DLT evaluable subjects for the AMG 596 in combination with AMG 404.**

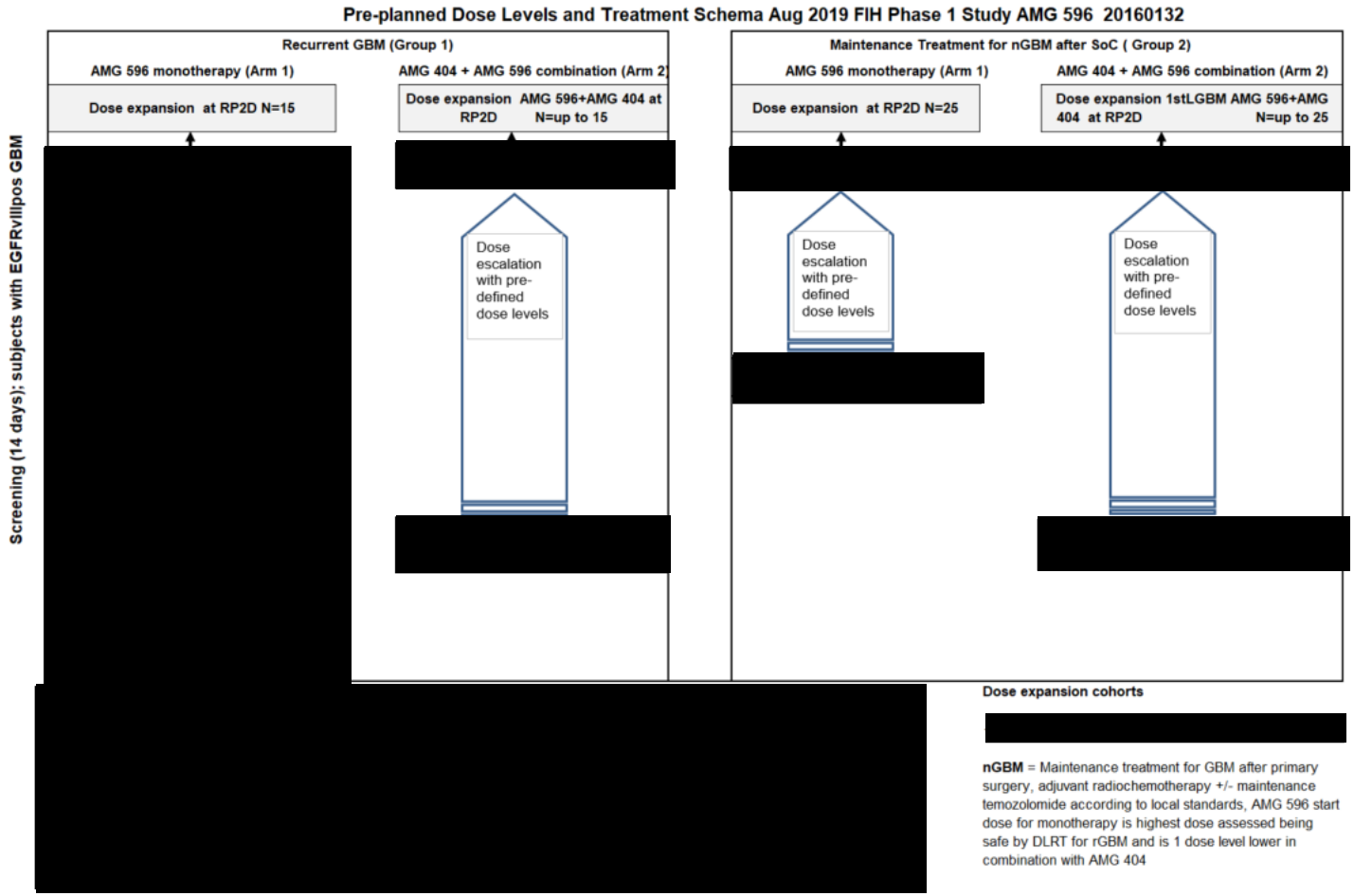
Section	Amended text
P6, Protocol Synopsis, Sample Size	Replace It is anticipated that around 82 subjects will be enrolled in the study. Up to 30 DLT-evaluable subjects will be enrolled in dose escalation in Group 1 (recurrent disease) and up to 12 subjects in dose escalation Group 2 (maintenance setting). Up to 40 subjects will be enrolled in the dose expansion cohorts (15 subjects in Group 1 and up to 25 subjects in Group 2) at 9 or more sites across US, Australia and Europe. With It is anticipated that around **190** subjects will be enrolled in the study, **up to 100 subjects will be enrolled to Arm 1 and up to 90 subjects will be enrolled to Arm 2. Enrollment for Arm 1 and Arm 2 will occur at 12 or more sites across US, Australia and Europe.**
P6, Protocol Synopsis, Sample Size	Add **For Group 1 (recurrent disease), the following are the planned sample sizes.** • **In dose escalation, up to 45 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 30 DLT-evaluable subjects to combination Arm 2** • **In dose expansion, up to 15 subjects will be enrolled to monotherapy Arm 1 and up to 15 subjects to combination Arm 2.** **For Group 2 (maintenance setting), the following are the planned sample sizes.** • **In dose escalation, up to 15 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 20 DLT-evaluable subjects to combination Arm 2** • **In dose expansion, up to 25 subjects will be enrolled to monotherapy Arm 1 and up to 25 subjects to combination Arm 2**
P6, Protocol Synopsis, Sample Size	Replace The sample size for Group 1 dose expansion is based on practical considerations. With **For both Arm 1 and Arm 2,** the sample size for Group 1 dose expansion is based on practical considerations.

Section	Amended text
P6, Protocol Synopsis, Sample Size	Replace With 21 subjects treated at Group 1 RP2D/MTD (6 from dose escalation and 15 from dose expansion), With With 21 subjects treated at the **respective** Group 1 RP2D/MTD (6 from dose escalation and 15 from dose expansion),
P6, Protocol Synopsis, Sample Size	Replace The sample size for Group 2 dose expansion is based on a Bayesian predictive probability design With **For both Arm 1 and Arm 2,** the sample size for Group 2 dose expansion is based on a Bayesian predictive probability design
P7, Protocol Synopsis, Investigational Product (IP)	Add **AMG 404**
P7 Protocol Synopsis Investigational Product	Add **AMG 404 is supplied in a 3 mL Type 1 glass tubing vial containing 1 mL deliverable volume of 70 mg/mL. The drug product is formulated with 10 mM acetate (sodium counterion), 9.0% (w/v) sucrose, 0.01% (w/v) polysorbate 80, pH 5.2 and will be prepared for IV administration by dilution.**
P7, Protocol Synopsis Investigational Product	Delete ~~Dose escalation Phase 1 only~~

Section	Amended text
P7, Protocol Synopsis Investigational Product	Add **AMG 404 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment. AMG 404 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines. The drug will be administered as an IV infusion at a constant flow rate over 30 minutes every [redacted].**
P7, Protocol Synopsis Investigational Product	Replace All subjects will be hospitalized for the first [redacted] of infusion and for at least 24 hours following completion of the infusion in cycle 1, and for 72 hours after a dose step in cycle 1, and at least for the first 72 hours of infusion in any subsequent cycle and after a dose step in any subsequent cycle. Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator With All subjects will be hospitalized **for the following periods:** **Cycle 1:** • **For the first [redacted] of AMG 596 monotherapy (Arm 1)** • **For the first [redacted] of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on [redacted]** • **For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2** • **For additional 72 hours after AMG 596 step dose if necessary** **Cycle 2 and all subsequent cycles:** • **For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2** • **For additional 72 hours after AMG 596 step dose if necessary.** **Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator.** **AMG 404 can be administered in an outpatient setting starting from cycle 1 [redacted] onwards. Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.**

Section	Amended text
P8, Protocol Synopsis Procedure	Add **or the combination of AMG 596 and AMG 404**
P8, Protocol Synopsis Procedure	Replace managing physician With **Investigator**
P8, Protocol Synopsis Procedure	Replace including serum pregnancy test, if applicable, coagulation, hematology, chemistry, urinalysis, hepatitis serology, human immunodeficiency virus (HIV) test, [redacted] With including serum pregnancy test, if applicable, coagulation, hematology, chemistry, urinalysis, hepatitis serology, human immunodeficiency virus (HIV) test, [redacted]
P8, Protocol Synopsis Statistical considerations	Replace In dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. In dose expansion for Group 2, futility will be assessed initially for N=10 and continuously afterwards using a Bayesian predictive probability design. With **For both Arm 1 and Arm 2,** in dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. **For both Arm 1 and Arm 2,** in dose expansion for Group 2, futility will be assessed initially for N=10 and continuously afterwards using a Bayesian predictive probability design.

Section	Amended text
P10. Protocol Synopsis, Figure one, study design and treatment schema	Replace **Pre-planned Dose Levels and Treatment Schema After July 2018 FIH Phase 1 Study AMG 596 20160132**  **Dose expansion cohorts** **rGBM** = relapsed glioblastoma **1stLGBM** = Maintenance treatment for GBM after primary surgery, adjuvant radiochemotherapy +/- maintenance temozolomide according to local standards

Section	Amended text
	With 
P13, Abbreviation	Add **mAb, Monoclonal antibody**

Section	Amended text
P22, Section 1.1	Replace Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and in the maintenance treatment phase of newly diagnosed glioblastoma (maintenance setting) (Group 2) With Evaluate the safety and tolerability of AMG 596 administered by continuous intravenous (cIV) infusion **in monotherapy (Arm 1) and in combination with AMG 404 (Arm 2)** in subjects with EGFRvIII-positive glioblastoma or malignant glioma in the recurrent setting (Group 1) and in the maintenance treatment phase of newly diagnosed glioblastoma (maintenance setting, Group 2)
P22, Section 1.2 Secondary Objective	Replace Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion With Evaluate the pharmacokinetics (PK) of AMG 596 in serum when administered by cIV infusion **either in monotherapy or in combination with AMG 404**
P22, Section 1.2 Secondary Objective	Add **Evaluate the pharmacokinetics (PK) of AMG 404 in serum when administered by short term infusion in combination with AMG 596**
P22, Section 1.2 Secondary	Replace Evaluate the clinical benefit of AMG 596 as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO) With Evaluate the clinical benefit of AMG 596 **monotherapy or AMG 596 in combination with AMG 404** as determined by objective response rate (ORR) per modified Response Assessment in Neuro-Oncology Criteria (RANO)

Section	Amended text
P22, Section 1.2 Secondary	Replace Evaluate progression free survival rate at 6 and 12 months after initiation of treatment With Evaluate progression free survival rate at 6 and 12 months after initiation of treatment **for any Part, Arm and Group of the study**
P22, Section 1.3 Exploratory	Replace [redacted] With [redacted]
P23, Epidermal Growth Factor Receptor Variant EGFRvIII	Add **Kischel et al., 2016**

Section	Amended text
P23, Epidermal Growth Factor Receptor Variant EGFRvIII	Add **and potent**
P23, Epidermal Growth Factor Receptor Variant EGFRvIII	Add **Cytotoxicity**
P24-26, Checkpoint inhibits for treatment of GBM	Add **Checkpoint inhibitors for treatment of Glioblastoma (GBM)** **Immunotherapies with checkpoint inhibitors have been explored in GBM with limited success (Omuro et al., 2018) and response rates have been rarely above 10 percent (Wang et al., 2019). Reasons for failure are associated with (1) genetic patterns supporting immunosuppressive tumor microenvironment, eg PTEN mutations leading to cell clustering and lack to increase T cell infiltration, (2) evolutionary patterns promoting negative selection of immunogenic neoepitopes, and (3) greater increase in T cell diversity leading to failure of selective recruitment of lymphocytes to tumor (Zhao et al., 2019).** **Nivolumab, a fully human IgG4 subtype programmed death-1 (PD-1) immune checkpoint inhibitor was evaluated in a large randomized clinical trial (Reardon et al., 2017) in monotherapy or combination with ipilimumab and monotherapy was compared versus bevacizumab in 369 patients with first recurrence of GBM in the phase 3 part (NCT02017717). At baseline, most patients in the nivolumab (nivo, 83%) and bevacizumab (bev, 84%) arms had measurable disease, and 40% (nivo) and 43% (bev) of patients required corticosteroids, receiving up to ≥ 4 mg/day. The 12-month OS was 42% in both monotherapy arms and median OS for nivolumab was 9.8 months compared to 10 months for bevacizumab. ORRs were 8% (nivo) and 23% (bev); median duration of response was 11.1 months (nivo) and 5.3 months (bev). Most common treatment-related AEs (≥ 10% of patients in either arm; nivo vs bev) were fatigue (21% vs 14%) and hypertension (1% vs 22%). Serious AEs (all causalities) were reported in 46% (nivo) and 35% (bev) of patients. Seizure (8% vs 6%) and malignant neoplasm progression (11% vs 7%) were the only serious AEs reported in ≥ 5% of patients in either arm.** **Pembrolizumab, a humanized IgG4 anti PD-1 monoclonal antibody (mAb), was explored in GBM in a basket**

Section	Amended text
	trial (Keynote-028) with the GBM basket of patients with any recurrence including two-thirds being treated after their first recurrence (Reardon et al., 2016). One partial response (ORR 4%) was observed within 25 patients and 12 patients (48%) presented with SD. Treatment-related AEs occurred in 19 (73.1%) patients, most commonly fatigue and rash (n=6 each, 23.1%). Four (15.4%) patients experienced grade 3–4 treatment-related AEs (lymphopenia, type 2 diabetes mellitus, arthritis, and syncope). Pembrolizumab in combination with bevacizumab was compared with pembrolizumab in 80 patients with recurrent GBM for the primary endpoint of 6-month PFS per RANO (NCT02337491). At a median follow-up of 25 months the 6-month PFS was 6.7% for pembrolizumab monotherapy and 25.3% for the combination (Reardon et al., 2018). Most commonly observed treatment-related AEs were headache (30%) and fatigue (17%) for pembrolizumab monotherapy. **Although PD-L1 expression has been reported in GBM specimen, the observed clinical results were discouraging (Berghoff et al., 2015). Emerging evidence of relevant immune cell activation through blockade of PD-1/PD-L1 axis comes from most recently published studies with neoadjuvant checkpoint blockade. Patients with recurrent GBM receiving neoadjuvant pembrolizumab prior to surgical debulking experienced significantly longer overall survival versus those receiving adjuvant, postsurgical pembrolizumab simply. In the neoadjuvant group, focal induction of PD-L1 in the tumor microenvironment and activation of tumor infiltrating lymphocytes, linked with upregulation of interferon gamma related genes suggesting relevant immune cell activation, were observed. Moreover, expanded T cell receptor clones correlating between tumor and blood with high overlap, and a decreasing monocytic population in the peripheral blood were associated with neoadjuvant pembrolizumab but not seen with adjuvant treatment only. Interestingly, dexamethasone was not found to impact upregulation of interferon gamma and T cell activation genes. Hence, only patients with baseline 4 mg/day or less dexamethasone was allowed to enroll. The authors concluded that an immune response leading to prolonged survival was induced by repeated PD-1 blockade whereby maintaining functionality of tumor-specific T cell clones, and by down-regulation of cell cycle related gene expression within tumor cells through T cell-mediated interferon gamma response (Cloughesy et al., 2019). A similar approach with neoadjuvant administration of nivolumab to patients undergoing surgery for GBM indicates the onset of antitumor-directed immune pharmacodynamic effects after treatment with neoadjuvant nivolumab (Schalper et al., 2019).** **Ultimately, to overcome hurdles for success of immunotherapies in GBM such as a limited number of infiltrated T cells and an upregulated immunosuppressive signature, the combination of checkpoint blockade with BiTE® treatment may be an alternative approach to achieve clinically meaningful tumor regression. The combination of checkpoint inhibitors with various BiTE® molecules in preclinical studies showed that cytotoxic potential, T cell activation and proliferation are strongly enhanced upon blockade of**

Section	Amended text
	the PD-1/PD-L1 axis (Kufer et al., 2016, Osada et al., 2015). The addition of AMG 404, an anti-PD-1 mAb that is being developed by Amgen, to AMG 596 may support maintaining T cell activation by blocking PD-1 upregulation on T cells and avoid T cell exhaustion facilitated by the immunosuppressive microenvironment. The current study with AMG 404 will enable a deeper understanding of synergistic efficacy, toxicity, and pharmacodynamic profiles of the combination of AMG 404 and AMG 596.
P26, Section 2.2 Amgen Investigational Product Background AMG 596	Add **AMG 596**
P26, Section 2.2 Amgen Investigational Product Background AMG 596	Replace [redacted] With [redacted]
P28-29, Section 2.3	Add **2.3 Amgen Investigational Product Background AMG 404** **2.3.1 Nonclinical Pharmacology** **AMG 404 is an IgG1 antibody; however, the Fc region has been modified to eliminate undesired interactions with Fc gamma receptors. The ligand blocking activity of AMG 404 was evaluated in three different assays using three different readouts and both cell-expressed, as well as recombinant, soluble ligands. In each assay, AMG 404 demonstrated the expected dose-dependent activity, indicating it is a potent inhibitor of human and cynomolgus monkey PD-1 binding.** **2.3.2 Nonclinical Pharmacokinetics** **The toxicokinetics (TK) of AMG 404 were characterized in a Good Laboratory Practice (GLP) study after weekly IV administration of [redacted] mg/kg or SC administration of [redacted] mg/kg for four consecutive weeks. Following repeat dose administration, AMG 404 exposure increased approximately dose-proportionally from**

Section	Amended text
	[redacted] mg/kg as measured by C_{max} and AUC over 6 days. AMG 404 exposures were similar between male and female animals. **2.3.3 Toxicology** **The potential for AMG 404 to cause acute release of cytokines from human peripheral blood leukocytes (PBL) in the presence of human endothelial cells (HUVECs) was evaluated in vitro. Under the conditions tested, AMG 404 did not induce cytokine release above background levels.** **AMG 404 was evaluated in a [redacted] GLP toxicology study in cynomolgus monkeys. Doses of [redacted] mg/kg were administered by slow IV bolus, and doses of [redacted] mg/kg were administered SC (3 animals/sex/group). Animals were dosed once weekly (4 total doses). There were no AMG 404-related clinical signs or effects on body weight, food consumption, respiratory rate, body temperature, organ weights, or urinalysis parameters and no AMG 404-related ocular, electrocardiographic, neurologic, or macroscopic findings. AMG 404-related clinical pathology changes were limited to mild decreases in lymphocytes for females at all dose levels on Day 2 that were generally similar to control and/or baseline values on Day 9 and throughout the remainder of the study, and mildly increased C-reactive protein in some animals.** **In conclusion, administration of AMG 404 by once weekly IV bolus or SC injection was well tolerated in cynomolgus monkeys at levels of [redacted] mg/kg IV and [redacted] mg/KG IV and SC.** **Refer to AMG 404 Investigators Brochure for more information.**
P29, Section 2.4.1 AMG 596 Monotherapy	Replace At this time, there is no clinical experience with AMG 596 in humans With At this time, there is **limited** clinical experience with AMG 596 in humans **derived from first 15 subjects treated in this study and data are summarized in the AMG 596 Investigator's Brochure.**

Section	Amended text
P29, Section 2.4.1 AMG 596 Monotherapy	Add **AMG 596**
P28-31 Section 2.4.1 AMG 596 Monotherapy	Add 

Section	Amended text
	[redacted]

Section	Amended text
P32, Section 2.5 Rationale	Add **2.5.1 Rationale for AMG 596 Monotherapy**
P32, Section 2.5 Rationale	Replace After establishing the maximum tolerated dose (MTD) or recommended phase dose (RP2D) in the recurrent setting With After **the observation of a first objective response (partial or complete)** in the recurrent setting,
P33-34, Section 2.5.2 Rationale for the Combination of AMG 596 with AMG 404	Add **2.5.2 Rationale for the Combination of AMG 596 with AMG 404** **BiTE treatment helps T cells to infiltrate tumor and become activated independent of the immunosuppressive microenvironment. However, preclinical evaluations showed that BiTE induced T cell activation is associated with upregulation of PD-1 on T cells, a known immune-regulatory mechanism that may lead to diminished T cell cytolytic activity resulting in impaired ability of T cells to eradicate the tumor. Anti-PD-1 therapy is intended to reverse this T cell exhaustion. Indeed, in vitro combination of AMG 596 with AMG 404 demonstrated more cytotoxic activity than AMG 596 alone.** **We hypothesize that the addition of an anti-PD-1 antibody, such as AMG 404, may help maintain AMG 596-induced tumor cell killing by T cells resulting in improved antitumor activity in the clinical setting.** **Initial signs of clinically meaningful antitumor effect with AMG 596 monotherapy in subjects with recurrent glioblastoma have been observed. In addition, monotherapy administration of both novel products, AMG 596 and AMG 404, has been well tolerated, to date. Moreover, tolerability of anti-PD-1 antibodies has been demonstrated in subjects with glioblastoma in various clinical trials (Reardon et al., 2017, Schalper et al., 2019, Kufer et al., 2016, Osada et al., 2015). Considering the devastating nature of glioblastoma, the addition of AMG 404 to AMG 596, even in this early stage of the development of both investigational products, can be justified and can contribute to enrichment of treatment opportunities.**
P34, Section 2.5.3 Dose Rationale	Add **2.5.3.1 AMG 596 Monotherapy**

Section	Amended text
P34, Section 2.5.3.1 AMG 596 Monotherapy	Delete ~~currently in development~~
P34, Section 2.5.3.1 AMG 596 Monotherapy	Add **Clinical PK data for AMG 596 can be found in the AMG 596 Investigator's Brochure.**
P34, Section 2.5.3.1 AMG 596 Monotherapy	Replace The predicted human steady-state concentration of AMG 596 after a [redacted] µg/day IV infusion was also found to be 20600-fold lower than the observed exposure in cynomolgus monkeys at the 6.6 mg/kg/day dose, accounting for a 7-fold difference in potency between human and monkey effector cells. With **At the starting dose of [redacted] µg/day, the safety margins based on the observed Css were 13 400-fold before potency adjustment and 1910-fold after correction for a 7-fold difference in AMG 596 potency between human and cynomolgus monkey effector cells.**
P34, Section 2.5.3.1 AMG 596 Monotherapy	Delete ~~The predicted human steady-state concentration of AMG 596 after a [redacted] µg/day IV infusion was also found to be 20600-fold lower than the observed exposure in cynomolgus monkeys at the 6.6 mg/kg/day dose, accounting for a 7-fold difference in potency between human and monkey effector cells.~~
P34, Section 2.5.3.1 AMG 596 Monotherapy	Add **A pharmacodynamic drug interaction study showed that AMG 596-induced cytokine release could be reduced by dexamethasone, but dexamethasone might result in a reduced cytotoxic potency of AMG 596 when co-administered to patients.**
P34, Section 2.5.3.1 AMG 596 Monotherapy	Add **Dose escalation in Group 2 subjects can start at the highest AMG 596 monotherapy dose deemed to be tolerated by DLRT for Group 1 subjects.**

Section	Amended text
P36-37, Section 2.5.3.2 AMG 596 in Combination with AMG 404	Add **2.5.3.2 AMG 596 in Combination with AMG 404** **No clinical safety information is available for the combination of AMG 596 with AMG 404. Based on biological mechanism of action and initial clinical safety information for monotherapies with AMG 596 and AMG 404, adverse events caused by synergistic activation of T cells are expected.** **The first-in-human dose exploration and expansion study evaluating AMG 404 in subjects with advanced solid tumors is currently ongoing. Preliminary PK results of AMG 404 in 11 subjects with advanced solid tumors after AMG 404 administration as short-term IV infusions (approximately 0.5 hours) [redacted] were available for dose levels of [redacted] mg (3 subjects, first and second dosing intervals) and [redacted] mg (8 subjects, first dosing interval). The nonclinical pharmacology findings and preliminary human PK results from the FIH study provide increased confidence towards achieving an efficacious dose with doses planned in the study and results were consistent with those for other therapeutic anti-PD-1 mAbs. Moreover, no dose-limiting toxicities (DLTs) were observed in any of the 12 subjects who have received AMG 404 doses up to [redacted] mg [redacted] Treatment-emergent adverse events were reported in 9 subjects (75.0%); the most frequently reported adverse events (≥ 3 subjects) were fatigue (4 subjects, 33.3%) and nausea (3 subjects, 25.0%). Three subjects (25.0%) had 5 adverse events that were grade 3 in severity (dehydration, edema, fatigue, urinary tract infection, and vomiting); no grade 3 adverse event preferred term was reported in > 1 subject.** **Since AMG 404 doses up to [redacted] mg administered every 4 weeks have been shown to be tolerable, with the only treatment-related adverse event occurring in > 1 subject of nausea in 2 subjects (16.7%), the highest dose explored ([redacted] mg) will be used for combination therapy with AMG 596. If a higher AMG 404 dose will be declared as recommended phase 2 dose in the ongoing Phase 1 study (Study 20180143), such a dose can be explored in additional cohort(s) in combination with AMG 596 whereby using the highest AMG 596 dose shown to be tolerated in the combination cohorts with AMG 404.** **For AMG 596, the start dose in combination with AMG 404 treatment is based on the observation of pharmacodynamic effects observed at [redacted] µg/day in Group 1 subjects with recurrent malignant glioma. For Group 1 subjects, a dose of [redacted] µg/day administered in [redacted] infusion cycles will therefore be selected as first dose. The next AMG 596 pre-defined doses will be used for further dose escalation.** **For Group 2 subjects, the starting dose of AMG 596 in combination with AMG 404 will be one dose level below the selected start dose for AMG 596 monotherapy (eg a start dose of [redacted] µg/day for AMG 596 monotherapy in Group 2 subjects leads to the selection of [redacted] µg/day as start dose for AMG 596 in combination with AMG 404 in Group 2 subjects). The next AMG 596 pre-defined doses will be used for further dose escalation.** **To avoid cumulative toxicity associated with initial T cell activation after treatment start, a first dose of AMG 404 will not be given until [redacted] after start of the AMG 596 infusion. Prophylactic dexamethasone treatment as described in Section 6.5, should be given before starting any AMG 596 infusion. Dose escalation will start with single subject cohorts as a pharmacodynamic effect is expected resulting in a reduced cytotoxic potency of AMG 596 when co-administered with dexamethasone.**

Section	Amended text
P37, Section 2.6 Hypotheses	Add **monotherapy and in combination with AMG 404**
P37, Section 2.6 Hypotheses	Add **monotherapy and/or in combination with AMG 404**
P37, Section 3.1 Study Design	Replace This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma. The study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). With This is a first in human (FIH), open-label, sequential-dose-escalation study in subjects with EGFRvIII-positive glioblastoma or malignant glioma **exploring AMG 596 monotherapy (Arm 1) and combination of AMG 596 and AMG 404 (Arm 2). Each arm of the** study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2).
P38, Section 3.1 Part 1: Dose Escalation	Replace The purpose of dose escalation is to make a preliminary estimate of the RP2D /MTD of AMG 596. Treatment is divided into 2 periods: (1) DLT period 1 for [redacted] of AMG 596 infusion and (2) DLT period 2 for day [redacted] of infusion. With The purpose of dose escalation is to make a preliminary estimate of the RP2D /MTD of AMG 596 **monotherapy and in combination with AMG 404.** Treatment is divided into 2 periods: (1) DLT period 1 for [redacted] of AMG 596 infusion and (2) DLT period 2 for [redacted] of **AMG 596** infusion **(applies for both Arms).**

Section	Amended text
P38, Section 3.1 Study Design, Part 1, Dose Escalation	Replace The start dose based on preclinical evaluations for the estimation of the MABEL is [redacted] µg/day. Further pre-specified nominal doses for use in the dose escalation are [redacted] µg/day. With The **AMG 596** start dose based on preclinical evaluations for the estimation of the MABEL is [redacted] µg/day. Further pre-specified nominal **AMG 596** doses for **potential** use in **any** dose escalation **Arms** are [redacted] µg/day.
P38, Section 3.1 Study Design, Part 1, Dose Escalation	Replace The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2) With The preliminary estimate of the RP2D/MTD of AMG 596 will be done initially in subjects with recurrent disease (Group 1) and **separately** in subjects with maintenance treatment after SoC in newly diagnosed disease (Group 2) **and separately for AMG 596 monotherapy and in combination with AMG 404.**
P38, Section 3.1 Study Design Part 1, Dose Escalation	Add **If same AMG 596 doses are to be explored in monotherapy and in combination, the monotherapy cohort must be completed before enrollment in the combination cohort.**
P38, Section 3.1 Study Design Part 1, Dose Escalation	Add **AMG 596**
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Delete ~~Dose Escalation in Group 1 will proceed using 2 phases~~

Section	Amended text
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Replace Dose Escalation Phase 1, single subject cohorts With Dose Escalation **in** single subject cohorts
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Add **AMG 596 monotherapy**
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Add **Combination of AMG 596 with AMG 404: The starting dose of AMG 596 is [redacted] ug/day administered in [redacted] cycles and the defined AMG 404 dose is [redacted] mg every 4 weeks.**
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Delete ~~The DLT period is [redacted]; DLT period 1 is from [redacted] of AMG 596 infusion, and DLT period 2 is from [redacted] of infusion (including cycle 2).~~

Section	Amended text

P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Replace
	• The cohort size will be increased to N=2-4 subjects (= Start of Dose Escalation Phase 2, multiple subject cohorts) after observation of
	  • Treatment-related adverse events of common terminology criteria for adverse events (CTCAE) grade 2 or higher and/or
	  • Quantifiable cytokine levels in blood or CSF above baseline
	With
	• The cohort size will be increased to N=2-4 subjects (= Start of multiple subject cohorts) after observation of
	  • Treatment-related adverse events of common terminology criteria for adverse events (CTCAE **4.0**) grade 2 or higher and/or
	  • Quantifiable cytokine levels in blood or CSF above baseline

P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Replace Dose Escalation Phase 2, multiple subject cohorts: • Subjects in the first multiple subject cohort receive the same dose as the last single subject cohort. • All subjects receive 28-day infusion cycles with 14-day treatment break until treatment discontinuation criteria apply. With Dose Escalation **in** multiple subject cohorts: • Subjects in the first multiple subject cohort receive the same dose as the last single subject cohort. • All subjects receive **AMG 596 in** [redacted] infusion cycles until treatment discontinuation criteria apply.
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Delete ~~In the first cycle, DLT period 1 is from~~ [redacted] ~~of AMG 596 infusion and DLT period 2 is from~~ [redacted] ~~of infusion.~~

Section	Amended text
P39, Section 3.1 Study Design, Group 1, Recurrent Disease	Replace The maximum total sample size of N=30 DLT evaluable subjects (including single subject cohorts) is reached. With The maximum total sample size of N=**45 DLT** evaluable subjects (including single subject cohorts) is reached for **AMG 596 monotherapy or N=30 DLT evaluable subjects for AMG 596 in combination with AMG 404.**
P40, Section 3.1, Study Design Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease	Replace A first cohort will start after RP2D/MTD has been established in Group 1 subjects with recurrent EGFRvIII-positive glioblastomas or malignant glioma. The starting dose in Group 2 will be decided by DLRT and will be the MTD of Group 1, With A first cohort will start after **observation of a first objective antitumor response** in Group 1 subjects with recurrent EGFRvIII-positive glioblastomas or malignant glioma. The starting dose of **AMG 596 monotherapy** in Group 2 will be decided by DLRT and **will be the current highest dose deemed safe** of Group 1,
P40, Section 3.1, Study Design Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease	Delete ~~or will be no higher than a 2-fold increase of the Group 1 RP2D if no MTD was reached and no DLT was observed at the highest dose administered in Group 1 dose escalation.~~
P40, Section 3.1, Study Design Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease	Add **The starting dose of AMG 596 in combination with AMG 404 for Group 2 will be one dose level below the selected start dose for AMG 596 monotherapy and an AMG 404 dose of [redacted] mg.**

Section	Amended text
P40, Section 3.1, Study Design Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease	Replace The cohort size will be N=4-6 subjects With The cohort size will be **N=2-4** subjects
P40, Section 3.1, Study Design Group 2, Maintenance Treatment after SoC in Newly Diagnosed Disease	Replace The maximum sample size of N=12 DLT evaluable subjects is reached With The maximum sample size of **N=15 DLT** evaluable subjects is reached **for AMG 596 monotherapy or N=20 DLT evaluable subjects for the AMG 596 in combination with AMG 404.**
P40, Section 3.1, Study Design, Dose Expansion	Replace It is anticipated that 15 subjects will be enrolled to Group 1 and up to 25 subjects will be enrolled to Group 2. With It is anticipated that 15 subjects will be enrolled to Group 1 **in Arm1 and Arm 2, respectively**. Up to 25 subjects will be enrolled to Group 2 **in Arm 1 and Arm 2, respectively**.
P41, Section 3.1, Study Design Dose Expansion	Replace In Group 2, the objective response rate (ORR) of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. With In Group 2 **both for Arm 1 and Arm 2**, the objective response rate (ORR) of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity.

Section	Amended text
P41, Section 3.1, Study Design Dose Expansion	Replace The ORR in Group 2 will be initially evaluated after 10 subjects are treated and have been evaluated at the first imaging scan or have dropped out before that. With **For each arm,** the ORR in Group 2 will be initially evaluated after 10 subjects are treated and have been evaluated at the first imaging scan or have dropped out before that.
P41, Section 3.1, Study Design Dose Expansion	Replace During dose expansion, Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached. With During dose expansion **and separately for the monotherapy arm (combining data from Groups 1 and 2) and for the combination arm (combining data from Groups 1 and 2),** Amgen will conduct evaluations of the ongoing grade 4 or higher treatment-related adverse event rate to assess if the threshold for possible early trial termination has been reached.

<table>
<tr><th>Section</th><th>Amended text</th></tr>
<tr><td>P41,
Section 3.1,
Study Design,
Dose Expansion</td><td>Replace
<table>
<tr><th>Number of subjects</th><th>Hold enrollment if observing this many grade 4 or higher treatment-related adverse events</th></tr>
<tr><td>10</td><td>≥ 4</td></tr>
<tr><td>20</td><td>≥ 6</td></tr>
<tr><td>30</td><td>≥ 9</td></tr>
<tr><td>35</td><td>Study Complete</td></tr>
</table>
With
<table>
<tr><th>Number of subjects</th><th>Hold enrollment if observing this many grade 4 or higher treatment-related adverse events</th></tr>
<tr><td>10</td><td>≥ 4</td></tr>
<tr><td>20</td><td>≥ 6</td></tr>
<tr><td>30</td><td>≥ 9</td></tr>
<tr><td>40</td><td>Study Complete</td></tr>
</table></td></tr>
</table>

Section	Amended text
P42, Section 3.1, Study Design, Dose Expansion, Figure 1. Schema of Study Design and Dosing Examples	Delete 

Section	Amended text
P42, Section 3.1, Study Design, Dose Expansion, Figure 2. Schema of Study Design and Dosing Examples	Add [redacted]
P43, Section 3.2 Number of Sites	Replace This study will be conducted at 12 sites in the United States, Australia and Europe. With This study will be conducted at **approximately** 12 **or more** sites in the United States, Australia and Europe.

Section	Amended text
P43, Section 3.3 Number of Subjects	Replace It is anticipated that around 82 subjects will be enrolled in the study. Up to 30 DLT-evaluable subjects will be enrolled in dose escalation in Group 1 (recurrent disease) and up to 12 subjects in Group 2 (maintenance treatment after SoC in newly diagnosed disease). Up to 40 subjects will be enrolled in the dose expansion cohorts at 9 or more sites in US, Australia and Europe. With It is anticipated that up to **190** subjects will be enrolled in the study**. It is anticipated that up to 100 subjects will be enrolled to Arm 1 in this study and up to 90 subjects will be enrolled to Arm 2 in this study.** **For Group 1 (recurrent disease), the following are the planned sample sizes.** • **In dose escalation, up to 45 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 30 DLT-evaluable subjects to combination Arm 2.** • **In dose expansion, up to 15 subjects will be enrolled to monotherapy Arm 1 and up to 15 subjects to combination Arm 2.** **For Group 2 (maintenance setting), the following are the planned sample sizes.** • **In dose escalation, up to 15 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 20 DLT-evaluable subjects to combination Arm 2** • **In dose expansion, up to 25 subjects will be enrolled to monotherapy Arm 1 and up to 25 subjects to combination Arm 2.**
P44, Section 3.4, Estimated Study Duration	Replace The duration of this study will be approximately 3.5 years, with about 36 months for enrollment (a maximum of 24 months for the dose escalation cohorts, and 12 months for the dose expansion cohort) and 6 months protocol treatment period. With The duration of this study will be approximately **4.5** years, with about **42** months for enrollment (a maximum of **30** months for the dose escalation cohorts, and 12 months for the dose expansion cohort) and **12** months protocol treatment period

Section	Amended text
P46, Section 4.2, Exclusion Criteria # 209	Add **Pembrolizumab**
P47, Section 4.2, Exclusion Criteria # 210	Replace Treatment with non-topical systemic corticosteroids within 14 days before enrollment (day 1) (exemption: systemic corticosteroid doses of ≤ 2 mg of dexamethasone (or equivalent) per day after consultation with Sponsor, exemption does not apply for Part 1 Dose Escalation Phase 1 subjects) With Treatment with non-topical systemic corticosteroids within 14 days before enrollment (day 1) (exemption: **prophylactic treatment with dexamethasone as defined in section 6.5,** and systemic corticosteroid doses of ≤ 2 mg of dexamethasone (or equivalent) per day after consultation with Sponsor,)
P47, Section 4.2, Exclusion Criteria # 214	Replace Male and female of reproductive potential who are unwilling to practice highly effective method(s) of birth control while on study through 1 week (5 half-lives) after receiving the last dose of study drug With Male and female of reproductive potential who are unwilling to practice highly effective method(s) of birth control while on study through **30 days** after receiving the last dose of **AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404**
P47, Section 4.2, Exclusion Criteria # 215	Replace Female who is lactating/breastfeeding or who plans to breastfeed while on study through 1 week (5 half-lives) after receiving the last dose of study drug. With Female who is lactating/breastfeeding or who plans to breastfeed while on study through **30 days** after receiving the last dose of **AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404.**

Section	Amended text
P47, Section 4.2, Exclusion Criteria # 217	Replace Female planning to become pregnant while on study through 1 week (5 half-lives) after receiving the last dose of study drug. With Female planning to become pregnant while on study through **30 days** after receiving the last dose of **AMG 596 and through 4 months (120 days) after receiving the last dose of AMG 404.**
P48, Section 4.2, Exclusion Criteria # 218	Replace Male who is unwilling to abstain from sperm donation while on study through 1 week (5 half-lives) after receiving the last dose of study drug. With Male who is unwilling to abstain from sperm donation while on study through **30 days** after receiving the last dose of AMG 596 **and through 4 months (120 days) after receiving the last dose of AMG 404**.
P48, Section 4.2 Exclusion Criteria	Add **The following Exclusion Criteria apply in addition for enrollment in combination cohorts with AMG 404** **220. History of solid organ transplantation.** **221. Prior treatment with anti-PD-1, anti-PD-L1, CTLA-4 or other checkpoint inhibitor drugs** **222. Prior treatment with AMG 596 monotherapy arm is not eligible to enroll in the combination therapy arm.** **223. Live vaccine therapies within 4 weeks prior to study drug administration** **224. Evidence of interstitial lung disease or active, non-infectious pneumonitis** **225. History of any immune-related colitis. Infectious colitis is allowed if evidence of adequate treatment and clinical recovery exists and at least 3 months interval observed since diagnosis of colitis.** **226. Active or history of any autoimmune disease or immunodeficiencies. Subjects with Type I diabetes, vitiligo, psoriasis, hypo-or hyper-thyroid disease not requiring immune-suppressive treatment are permitted.** **227. Myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or cardiac arrhythmia requiring medication.**

Section	Amended text
P50, Section 5.1 Treatment Assignment	Delete ~~Study Part 1, dose escalation, will start in Group 1 subjects and after establishing the RP2D in Group 1 dose escalation will proceed in Group 2 subjects. In Part 1 Dose escalation Phase 1, the initial dose escalation cohorts, only a single subject will be enrolled to a cohort because the dose level is not anticipated to be clinically active. The cohort size will be extended to 2 to 4 subjects, on a limited basis up to 5 subjects, in Part 1 Dose escalation Phase 2, when treatment-related adverse events of CTCAE grade 2 of higher and/or quantifiable cytokine levels in blood or CSF and above baseline are observed.~~ ~~Next cohorts (which are expected to be pharmacodynamically or clinically efficacious based on nonclinical models), will enroll up to 4 evaluable subjects. When a first DLT is observed, the BLRM will be used to guide dose level selection. The cohort size will be N=4-6 subjects for dose escalation in Group 2.~~ Add **Subjects will be treated either with AMG 596 monotherapy or with the combination of AMG 596 and AMG 404 in the respective treatment arm according their individual eligibility and availability of treatment slots. If AMG 596 dose are different, mono- and combination therapy cohorts can run in parallel. If same AMG 596 doses will be explored in monotherapy and in combination, the monotherapy cohort must be completed before enrollment in the combination cohort. Enrollment of Group 2 subjects can start after observation of a first objective response during Group 1 dose escalation.**
P50, Section 5.1 Treatment Assignment	Add **or AMG 596 in combination with AMG 404**
P50, Section 5.1 Treatment Assignment	Add **The Sponsor will provide the exact treatment assignment (cohort) to sites including AMG 596 or AMG 596 and AMG 404 doses and schedule.**

Section	Amended text
P51, Section 6.1, Classification of Product(s), Medical Device(s), and/or Combination Product(s)	Replace The Amgen IPs used in this study include AMG 596 and intravenous solution stabilizer (IVSS). With The Amgen IPs used in this study include AMG 596**, AMG 404** and intravenous solution stabilizer (IVSS).
P51, Section 6.1, Classification of Product(s), Medical Device(s), and/or Combination Product(s)	Replace The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 596. With The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of AMG 596 **and AMG 404**.
P52, Section 6.2.1.1 Dosage, Administration and Schedule for AMG 596	Replace Dosage, Administration and Schedule With Dosage, Administration and Schedule **for AMG 404**

Section	Amended text
P52, Section 6.2.1.1 Dosage, Administration, and Schedule for AMG 596	Add **AMG 596 administration can cause dose dependent increase of peritumoral edema leading to development or worsening of depressed level of consciousness, a disease related event, which can be prevented by prophylactic administration of dexamethasone. Prophylactic use of corticosteroids is mandated for any subject receiving a new cycle of AMG 596 (28 day on and 14 days off), with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) given within 1 hour prior to administration of AMG 596 and a second dose of dexamethasone given 8 mg IV 12 hours after start of the infusion. Subsequently, corticosteroids can be tapered at the discretion of the investigator based on clinical judgement. Same prophylactic use of dexamethasone is mandated for AMG 596 in combination with AMG 404 prior to the start of the AMG 596 infusion.** **Prophylactic treatment with steroid (eg, dexamethasone) is also mandated before restarting of AMG 596 or otherwise clinically indicated (see Section 6.2.4.1 and Section 6.3.2).**
P52, Section 6.2.1.1 Dosage, Administration, and Schedule for AMG 596	Replace Subjects will be hospitalized for the first 7 days of infusion and for at least 24 hours following completion of the infusion in cycle 1, and for 72 hours after a dose step in cycle 1, and at least for the first 72 hours of infusion in any subsequent cycle and after a dose step in any subsequent cycle. With Subjects will be hospitalized for **the following periods:** **Cycle 1:** • **For the first [redacted] of AMG 596 monotherapy (Arm 1)** • **For the first [redacted] of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on [redacted]** • **For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2** • **For additional 72 hours after AMG 596 step dose if necessary** **Cycle 2 and all subsequent cycles:** • **For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2** • **For additional 72 hours after AMG 596 step dose if necessary.**

Section	Amended text
P53, Section 6.2.1.1 Dosage, Administration, and Schedule for AMG 596	Replace The start dose based on preclinical evaluations for the estimation of the MABEL is [redacted] µg per day. Further pre-planned dose levels are [redacted] µg per day; step-dosing can be introduced. With The start dose **for AMG 596** based on preclinical evaluations for the estimation of the MABEL is [redacted] µg per day. Further **AMG 596** pre-planned dose levels are [redacted] µg per day; step-dosing can be introduced.
P53, Section 6.2.1.1 Dosage, Administration, and Schedule for AMG 596	Replace Intra-subject dose escalation will be allowed to higher dose levels in subsequent treatment cycles once a higher dose has been deemed safe by the DLRT With Intra-subject dose escalation **for AMG 596** will be allowed to higher dose levels in subsequent treatment cycles once a higher dose has been deemed safe by the DLRT.
P52, Section 6.2.1.1 Dosage, Administration, and Schedule for AMG 596	Replace A new cycle may begin +/- 2 days from the scheduled day 1 of the new cycle for logistical reasons. With A new cycle **for AMG 596** may begin +/- 2 days from the scheduled day 1 of the new cycle for logistical reasons.

Section	Amended text
P55, Section 6.2.2. Amgen Investigational Product AMG 404	Add **6.2.2 Amgen Investigational Product AMG 404** **AMG 404 is supplied in a 3 mL Type 1 glass tubing vial containing 1 mL deliverable volume of 70 mg/mL. The drug product is formulated with 10 mM acetate (sodium counterion), 9.0% (w/v) sucrose, 0.01% (w/v) polysorbate 80, pH 5.2 and will be prepared for IV administration by dilution.** **6.2.2.1 Dosage, Administration, and Schedule** **The investigational product will be dispensed at the research facility by a qualified staff member.** **At the beginning of a treatment cycle a physician or nurse trained in emergency medical care must be available when the infusion of investigational product is started for immediate intervention in case of complications.** **AMG 404 will be delivered using infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment.** **AMG 404 solution for infusion will be prepared in bags for IV infusion and delivered through infusion lines.** **The drug will be administered as an IV infusion at a constant flow rate over 30 minutes every [redacted] Subjects will be hospitalized for 24 hours after first administration of AMG 404 in Cycle 1 [redacted] of the AMG 596 infusion and should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each following AMG 404 infusion. Assessments should be performed as indicated in the Schedule of Activities.** **The planned dose, start date, start time, stop date, stop time, dose administered, reason for dose change, and package lot number of AMG 404 are to be recorded on each subject's eCRF(s) and/or the site's study files.** **6.2.2.2 Overdose** **The effect of overdose of this product are not known.**

Section	Amended text
P56, Section 6.2.3 Dose Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs)	Replace 6.2.3 Dose-cohort study Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs) With 6.2.3 Dose Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs)
P56, Section 6.2.3 Dose Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs)	Replace A DLT will be defined as any of the following occurring in a subject during the DLT period and regarded to be related to AMG 596. With A DLT will be defined as any of the following occurring in a subject during the DLT period **(first ■ treatment days for both AMG 596 monotherapy and in combination with AMG 404)** and regarded to be related to AMG 596 **and/or AMG 404.**
P56, Section 6.2.3 Dose Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs)	Add **Lymphopenia of any grade is not considered a DLT**
P56, Section 6.2.3 Dose Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs)	Add **Laboratory parameters of grade ≥ 3, not considered clinically relevant, and improved to grade ≤ 2 within 72 hours will not be considered DLT (for ALT and GGT elevations grade ≥ 3, not considered clinically relevant, and improved to grade ≤ 2 within 7 days due to the long half-life of these parameters)**

Section	Amended text
P56, Section 6.2.3 Dose Escalation, Stopping Rules and Dose-Limiting Toxicities (DLTs)	Add **Any grade 3 endocrinopathy that cannot be adequately controlled by hormonal replacement**
P57, Section 6.2.4, Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation	Replace Prophylactic treatment with steroid (eg, dexamethasone) is recommended before restarting of AMG 596 if clinically indicated. With Prophylactic treatment with steroid (eg, dexamethasone) is **mandated** before restarting of AMG 596**.**
P59, Table 3, Hematological Criteria for Dose Reduction	Replace **Table 2. Hematological Criteria for Dose Reduction** With **Table** 3. **Hematological Criteria for Dose Reduction**
P60, Table 4, Non-hematological Criteria for Dose Reduction	Replace Table 3, Non-hematological Criteria for Dose Reduction With Table **4**, Non-hematological Criteria for Dose Reduction

Section	Amended text
P60, Section 6.2.4.2 AMG 404 Dose Delay or Dose Reduction	Add **6.2.4.2 AMG 404** **Dose Delay or Dose Reduction** **Each subject will stay on the dose level assigned until treatment needs to be stopped. The reason for dose withholds and dose delays is to be recorded on each subject's CRF. Specific guidance for management of adverse events associated with AMG 404 are provided in Appendix G** **Immune-related Adverse Reactions** **Adverse events following the administration of AMG 404 may represent an immunologic etiology. Based on clinical experience with other anti-PD-L1 therapies, these immune-related toxicities may occur shortly after the first dose to several months after the last dose of treatment and may affect more than one body system simultaneously. Early recognition and management is critical to reduce complications.** **Most immune-related adverse events require adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests, such as bronchoscopy, endoscopy, or skin biopsy, may be included as part of the evaluation.** **Based on the type and severity of the immune-related adverse event, withholding or permanent discontinuation of AMG 404 may be required, in addition to treatment with corticosteroids and/or other therapies. Dose modification and toxicity management guidelines for immune-related adverse reactions are provided in Appendix G.** **Infusion-related Reactions** **Infusion-related reactions may occur with the administration of AMG 404. Monitor patients for signs and symptoms of infusion-related reactions, including pyrexia, chills, rigors, flushing, urticaria, hypotension, dyspnea, wheezing, headache, back pain, and abdominal pain. If an infusion-related reaction is suspected, perform a physical examination, monitor vital signs, monitor pulse oximetry, and perform and ECG if the patient is experiencing chest pain or sustained tachycardia.** **For mild or moderate infusion-related reactions, interrupt or slow the rate of infusion. For severe or life-threatening infusion-related reactions, permanently discontinue AMG 404. Treatment guidelines for infusion reactions associated with the administration of AMG 404 are provided in Appendix H.**

Section	Amended text
P61, Section 6.2.5 Permanent Discontinuation	Replace 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 (see Section 6.3 and Appendix E). With Dose-limiting or other unmanageable toxicity. **For exemption, please see section 6.2.3.**
P61, Section 6.2.5 Permenant Discontinuation	Replace Occurrence of neurologic-related adverse event considered related to AMG 596 by the investigator and meeting one or more of the following criteria: With Occurrence of neurologic-related adverse event considered related to AMG 596 **and/or AMG 404** by the investigator and meeting one or more of the following criteria
P61, Section 6.2.5 Permenant Discontinuation	Replace Occurrence of acute kidney injury considered related to AMG 596 by the investigator. With Occurrence of acute kidney injury considered related to AMG 596 **and/or AMG 404** by the investigator
P61, Section 6.2.5 Permanent Discontinuation	Add **Pregnancy**
P61, Section 6.2.5 Permanent Discontinuation	Add • **A DLT leads to permanent discontinuation unless the following criteria apply, in which case a restart of treatment at the same or a lower dose may be allowed:** – **The AE (including relevant lab values) is reversible and improves to grade ≤ 1 or baseline within 14 days** – **The patient is experiencing clinical benefit as assessed by the investigator** – **There is agreement between the investigator and the Amgen Medical Monitor that treatment may be restarted** – **The subject is willing to continue treatment after the investigator has led an appropriate discussion of potential risks and benefits with the subject**

Section	Amended text
P61, Section 6.2.5 Permanent Discontinuation	Delete ~~Male with pregnant partners or whose partners become pregnant while the subject is on study through 5 half-lives after receiving the dose of study drug must practice sexual abstinence or use a condom while on study through 5 half-lives after receiving the last dose of study drug.~~ ~~Female who becomes pregnant while on study through 5 half-lives after receiving the last dose of study drug will not receive subsequent scheduled doses and will be followed for safety until the safety follow up visit.~~
P62, Section 6.3.1, Cytokine Release Syndrome	Replace Subjects may be at an increased risk for cytokine release syndrome during the first few days following the initial infusion of AMG 596. With Subjects may be at an increased risk for cytokine release syndrome during the first few days following the initial infusion of AMG 596 **and/or AMG 404**.
P62, Section 6.3.1, Cytokine Release Syndrome	Replace Throughout the infusion with AMG 596, monitor subjects for clinical signs With Throughout the infusion with AMG 596 **and/or AMG 404**, monitor subjects for clinical signs

<table>
<tr><td>Section</td><td>Amended text</td></tr>
<tr><td>P65, Table 5, Management of Neurologic Events (by Severity)</td><td>Replace
Table 4. Management of Neurologic Events (by Severity)
<table>
<tr><th>CTCAE Grade</th><th>Intervention</th><th>Instructions for Infusion Interruption or Permanent Discontinuation</th></tr>
<tr><td>3</td><td>Perform physical exam, assess vital signs and conduct safety laboratory tests
Depending on the nature of the adverse event, additional measures (eg, CSF investigations, contrast-enhanced MRI of the head) can be taken upon discretion of the investigator
MRI should also be considered for subjects who permanently discontinue treatment at the discretion of investigator</td><td>Immediately interrupt AMG 596
Restart within 2 weeks, but not earlier than 72 hours (3 days) after the infusion has stopped, if the event resolves to grade ≤ 1 within 7 days
Permanently discontinue AMG 596 and AMG 404 if considered by the investigator related to study drug and if there is no improvement to grade ≤ 1 within 7 days</td></tr>
<tr><td>4</td><td>Perform physical exam, assess vital signs and conduct safety laboratory tests
Depending on the nature of the adverse event, additional measures (eg, CSF investigations, contrast-enhanced MRI of the head) can be taken upon discretion of the investigator
Conduct MRI for subjects who permanently discontinue treatment</td><td>Immediately interrupt AMG 596
Permanently discontinue AMG 596.</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Section</td><td>Amended text</td></tr>
<tr><td></td><td>With
Table 5. Management of Neurologic Events (by Severity)
<table>
<tr><th>CTCAE Grade</th><th>Intervention</th><th>Instructions for Infusion Interruption or Permanent Discontinuation</th></tr>
<tr><td>3</td><td>Perform physical exam, assess vital signs and conduct safety laboratory tests
Depending on the nature of the adverse event, additional measures (eg, CSF investigations, contrast-enhanced MRI of the head) can be taken upon discretion of the investigator
MRI should also be considered for subjects who permanently discontinue treatment at the discretion of investigator</td><td>Immediately interrupt AMG 596
Restart AMG 596 infusion within 2 weeks, but not earlier than 72 hours (3 days) after the infusion has stopped, if the event resolves to grade ≤ 1 within 7 days
Delay AMG 404 dosing until day 8 after AMG 596 restart if AMG 404 dosing was scheduled during interruption
Permanently discontinue AMG 596 and AMG 404 if considered by the investigator related to study drug and if there is no improvement to grade ≤ 1 within 7 days</td></tr>
<tr><td>4</td><td>Perform physical exam, assess vital signs and conduct safety laboratory tests
Depending on the nature of the adverse event, additional measures (eg, CSF investigations, contrast-enhanced MRI of the head) can be taken upon discretion of the investigator
Conduct MRI for subjects who permanently discontinue treatment</td><td>Immediately interrupt AMG 596
Permanently discontinue AMG 596 and AMG 404</td></tr>
</table></td></tr>
<tr><td>P64, Section 6.3.2, Infusion Interruption/Dose Modification due to Neurologic Events, Depressed Level of Consciousness</td><td>Replace
In case of occurrence of seizure grade 3, the infusion of AMG 596 will have to be stopped immediately

With
In case of occurrence of seizure grade 3, the investigational products will have to be stopped immediately</td></tr>
</table>

Section	Amended text
P64, Section 6.3.2, Infusion Interruption/Dose Modification due to Neurologic Events, Depressed Level of Consciousness	Add **Depressed level of consciousness** **Depressed level of consciousness is a common neurological sign of intracranial pressure increase. AMG 596 may cause inflammation at the site of the tumor, leading to worsening of increased intracranial pressure resulting in neurological toxicity including a depressed level of consciousness.** **Prophylactic use of corticosteroids is mandated for any subject receiving a new cycle of AMG 596 ([redacted]), with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) given within 1 hour prior to administration of AMG 596 and the second dose of dexamethasone 8 mg IV given 12 hours after start of the infusion, and subsequent tapering at the discretion of the investigator. Prophylactic treatment with steroid (eg, dexamethasone) is also mandated before restarting of AMG 596 or otherwise clinically indicated (see Section 6.3).**
P67, Section 6.3.4 Criteria for Permanent Withholding of Amgen Investigational Product due to Potential Hepatotoxicity	Replace Investigational product With **Both** investigational product**s**
P67, Section 6.3.4 Criteria for Conditional Withholding of Amgen Investigational Product due to Potential Hepatotoxicity	Replace Investigational product With Investigational product**s**

Section	Amended text
P69, Section 6.3.5, Criteria for Conditional Withholding of Amgen Investigational Products due to Potential Hepatotoxicity	Replace AMG 596 should be withheld pending investigation into alternative causes of DILI. With AMG 596 **and AMG 404** should be withheld pending investigation into alternative causes of DILI.
P69, Section 6.5 Concomitant Therapy	Add **Prophylactic use of corticosteroids is mandated for any subject receiving a new cycle of AMG 596 [redacted]), with dexamethasone 8 mg IV (or equivalent dose of other corticosteroids) given within 1 hour prior to administration of AMG 596 and the second dose of dexamethasone 8 mg IV given 12 hours after start of the infusion, and subsequent tapering at the discretion of the investigator. Same prophylactic use of dexamethasone is mandated for AMG 596 in combination with AMG 404 prior to the start of the AMG 596 infusion.** **Prophylactic treatment with steroid (eg, dexamethasone) is also mandated before restarting of AMG 596 or otherwise clinically indicated (see Section 6.3.1 and Section 6.3.2).**
P70, Section 6.6 Medical Device	Delete ~~Preprogrammed~~
P70, Section 6.6 Medical Device	Replace The investigational product must be administered using preprogrammed 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, concentrate for solution for infusion, will be prepared in bags for IV infusion and delivered through infusion lines with a 0.2 µm in-line filter. Both are compatible with the investigational product as described in the IPIM. Additional details for the use of the IV bag and infusion lines and their specifications are provided in the IPIM. With The investigational product**s** 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 and **as specified in Section 6.2.1 and Section 6.2.2** Investigational product**s**, concentrates for solution for infusion, will be prepared in bags for IV infusion and **AMG 596 will be** delivered through infusion lines with a 0.2 µm in-line filter. Both are compatible with the investigational product as described in the **respective** IPIM

Section	Amended text
P70, Section 6.6 Medical Device	Add **respective**
P70, Section 6.8 Excluded Treatments	Replace 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, other immunosuppressive therapies corticosteroids with exceptions as described in Section 6.3 and as described in Section 6.5 for management of CRS or neurologic adverse events With Any anti-tumor therapy other than the investigational products **are not permitted**, including cytotoxic and/or cytostatic drugs, hormonal therapy **(unless treatment for endocrinopathy)**, immunotherapy or any biological response modifiers, any other investigational agent, other immunosuppressive therapies. **C**orticosteroids **are** exceptions as described in Section 6.3 and Section 6.5 for management of CRS or neurologic adverse events.
P70, Section 6.8 Excluded Treatments	Add **Subjects who received AMG 596 as monotherapy are not allowed to participate in the combination therapy with AMG 404.**
P80, Section 7.1, Schedule of Assessments, Table 10	Add **Table 10. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 1 (Arm 2, Combination Therapy)**
P82, Section 7.1, Schedule of Assessments Table 10 Footnote	Replace Hospitalization at start of cycle 1 will be for a minimum of 7 days from the start of the infusion, and for at least 24 hours following completion of the infusion, and for 72 hours after a dose step at cycle 1 (if applicable) With Hospitalization at start of cycle 1 will be for a minimum of **8** days from the start of the **AMG 596** infusion**, whereby AMG 404 will be administered on** [redacted] and for at least 24 hours following completion of the **AMG 596** infusion. **All subjects will be hospitalized for at least** 72 hours after a dose step of AMG 596 at cycle 1 (if applicable). **Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1** [redacted] **onwards.**

Section	Amended text
P82, Section 7.1, Schedule of Assessments Table 10, Footnote	Add [k], **ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.**
P83, Section 7.1, Schedule of Assessments, Table 11	Add **Table 11, Schedule of Assessments Dose Escalation Cohort [redacted] AMG 596 Cycle 2 (AMG 404 3rd Infusion), Cycle 4 and all Subsequent Even Number Cycles (Arm 2, Combination Therapy)**
P85, Section 7.1, Schedule of Assessments Table 11 Footnote	Replace Hospitalization at start of cycle 1 will be for a minimum of 7 days from the start of the infusion, and for at least 24 hours following completion of the infusion, and for 72 hours after a dose step at cycle 1 (if applicable) With For combination therapy, hospitalization at start of cycle **2 and all subsequent cycles, and after dose step (if applicable) at cycle 2 and all subsequent cycles, will be for a minimum of 72 hours after start of AMG 596 until cycle 5. Hospitalization will be at a minimum of 48 hours after start of AMG 596 from cycle 6 onwards (per investigator's discretion). Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.**
P85, Section 7.1, Schedule of Assessments Table 11 Footnote	Add [k], **ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.**
P86, Table 12	Add **Table 12. Schedule of Assessments Dose Escalation Cohort [redacted] Infusion Cycle 3, and all Subsequent Odd Number Cycles (Arm 2, Combination Therapy)**

Section	Amended text
P85, Section 7.1, Schedule of Assessments Table 11 Footnote	Replace Hospitalization at start of cycle 1 will be for a minimum of 7 days from the start of the infusion, and for at least 24 hours following completion of the infusion, and for 72 hours after a dose step at cycle 1 (if applicable) With For combination therapy, hospitalization at start of cycle **2 and all subsequent cycles, and after dose step (if applicable) at cycle 2 and all subsequent cycles, will be for a minimum of 72 hours after start of AMG 596 until cycle 5. Hospitalization will be at a minimum of 48 hours after start of AMG 596 from cycle 6 onwards (per investigator's discretion). Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.**
P88, Section 7.1, Schedule of Assessments, Table 12 Footnote	Add [k], **ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.**
P93, Section 7.1, Schedule of Assessments, Table 15	Add **Table 15. Schedule of Assessment Dose Expansion Cohort [redacted] Cycle 1 and all Subsequent Odd Number Cycles (Arm 2, Combination Therapy)**

Section	Amended text
P95, Section 7.1, Schedule of Assessments, Table 15 Footnote	Add **EOI = End of Infusion; EOT = End of Treatment; LTFU = Long Term Follow Up; SCR = Screening; SFUP = Safety Follow Up** **[a] Hospitalization at start of cycle 1 will be for a minimum of 8 days from the start of the AMG 596 infusion, whereby AMG 404 will be administered on [redacted] and for at least 24 hours following completion of the AMG 596 infusion. All subjects will be hospitalized for at least 72 hours after a dose step of AMG 596 at cycle 1 (if applicable). Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.** **[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.** **[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.** **[d] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal.** **[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.** [redacted] **[g] If a subject discontinues after C1 this visit assessments will be considered EOT assessments. After EOT, please perform SFUP assessments as in Table 16.** [redacted] **[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.** **[j], ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.**
P96, Section 7.1, Schedule of Assessments Table 16,	Add **Table 16. Schedule of Assessment Dose Expansion cohort [redacted] Cycle 2 and all Subsequent Even Number Cycles (Arm 2, Combination Therapy)**

Section	Amended text
P98, Section 7.1, Schedule of Assessments Table 16 Footnote	Add **[a] For combination therapy, hospitalization at start of cycle 2 and all subsequent cycles, and after dose step (if applicable) at cycle 2 and all subsequent cycles, will be for a minimum of 72 hours after start of AMG 596 until cycle 5. Hospitalization will be at a minimum of 48 hours after start of AMG 596 from cycle 6 onwards (per investigator's discretion)., Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards** **[b] Clinical evaluations will include physical exam, ECOG, and weight. Screening only: demographics, medical/surgical history, and height will also be obtained.** **[c] Vital Signs will be repeated at least every 4 hours during the first 24 hours of infusion and every 6 hours during the minimum hospitalization period in each cycle. Vital signs will also be assessed prior to subject`s discharge from hospital in order to detect possible signs and symptoms of infusion reactions.** **[d] Serum pregnancy test will be performed for all females unless surgically sterile or ≥ 2 years postmenopausal** **[e] Radiological Assessment by MRI for tumor staging by modified RANO will be performed at screening (within 14 days of enrollment). If available, data from a prior imaging evaluation (historical data will be dated within 6 months of enrollment) will be entered at screening. Scans will include T2-weighted, T2/FLAIR, T1-weighted pre- and post-contrast enhanced and DW (selected sites only) images of the brain. All other known sites of disease should also be recorded and assessed.** [redacted] **[h] Safety Follow Up to be performed 30 days (+/- 7 days) after EOT.** **[i] Adverse events are to be collected for an eligible subject once the subject is enrolled in the study. A subject is considered enrolled after meeting all eligibility criteria and treatment and cohort have been assigned. Adverse events occurring during the screening period will be documented as medical history.** **[j] Medications associated with AEs or SAEs occurring between the SFUP visit and End of Study must also be collected.** **[k], ACTH to be done every 8 weeks (prior to cycles 1, 3, etc). ANA and ANCA (cytoplasmic and perinuclear) to be done at screening and then if clinically indicated.**
P99, Section 7.2, General Study Procedures	Replace During the study, every effort should be made to perform the study procedures as indicated on the Schedules of Assessments (Section 7.1, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10). With During the study, every effort should be made to perform the study procedures as indicated on the Schedules of Assessments (Section 7.1, Table 6, Table 7, Table 8, Table 9, Table 10**, Table 11, Table 12, Table 13, Table 14, Table 15, and Table 16).**

Section	Amended text
P99, Section 7.2, General Study Procedures	Replace A dose step can be introduced on [redacted] of a cycle, and assessments for the first week of the step dose (day 8 to day 14) must follow assessments for [redacted] of a cycle except for the pregnancy test. With **AMG 596** dose step can be introduced on [redacted] of a cycle, and assessments for the first week of the step dose ([redacted]) must follow assessments for [redacted] of a cycle except for the pregnancy test. **In case of step dosing, AMG 404 will be administered [redacted] after the AMG 596 target dose is achieved in cycle 1.**
P99, Section 7.2, General Study Procedures	Add **AMG 404 will be given every [redacted] ECG triplicate measurements will be performed during first AMG 404 infusion at pre-dose, EOI, and 4 hours after end of infusion for cycle 1. In all subsequent AMG 404 dose, ECG triplicate measurements will only be collected at predose and EOI.**
P99, Section 7.2, General study procedures	Replace Blood samples must not be taken/drawn from the catheter port used for AMG 596 infusion With Blood samples must not be taken/drawn from the catheter port used for AMG 596 **or AMG 404** infusion
P99, Section 7.2, General Study Procedures, Acceptable Deviation Windows	Add **After completion of cycle 1 (AMG 596 and AMG 404), +/- 1 day for all visits if logistically necessary**

<table>
<tr><th>Section</th><th>Amended text</th></tr>
<tr><td>P101, Section 7.2, General Study Procedures Table 17 List of Analytes</td><td>Replace
<table>
<tr><th>Chemistry</th><th>Hematology</th><th>Coagulation</th><th>Urinalysis</th><th>Other</th></tr>
<tr><td>Sodium
Potassium
Chloride
Bicarbonate (HCO3) or carbon dioxide
Total protein
Albumin
Glucose
Blood urea nitrogen or Urea
Creatinine
Total creatine kinase
Total bilirubin (TBL)
Direct bilirubin
Alkaline phosphatase (ALP)
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)</td><td>Hemoglobin
Hematocrit
Mean corpuscular volume
Platelets
White blood cell differential
• Total neutrophils
• Eosinophils
• Basophils
• Lymphocytes
• Monocytes</td><td>PT
PTT
INR
Fibrinogen
AT III</td><td>Specific gravity
pH
Blood
Protein
Glucose
Bilirubin
Microscopic exam** (performed at the discretion of the Investigator)</td><td>C-reactive protein (CRP)
IL-6
Serum Pregnancy
HLA typing
Hepatitis B surface antigen
Hepatitis C antibody
HIV*</td></tr>
</table></td></tr>
</table>

Section	Amended text
	With

Chemistry	**Hematology**	**Coagulation**	**Urinalysis**	**Other**
Sodium Potassium Chloride Bicarbonate (HCO3) or carbon dioxide Total protein Albumin **Calcium** **Calcium corrected** Glucose Blood urea nitrogen or Urea Creatinine **Estimated CrCl GFR, MDRD calculation** Total creatine kinase Total bilirubin (TBL) Direct bilirubin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) **TSH***** **Free T4***	**RBC** Hemoglobin Hematocrit Mean corpuscular volume **(MCV)** Platelets White blood cell differential • Total neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	PT PTT INR Fibrinogen AT III	Specific gravity pH Blood Protein Glucose Bilirubin Microscopic exam** (performed at the discretion of the Investigator)	C-reactive protein (CRP) IL-6 Serum Pregnancy HLA typing Hepatitis B surface antigen Hepatitis C antibody HIV* **ACTH***** **ANA***** **ANCA***** **(cytoplasmic and perinuclear)**

Section	Amended text
P99, P102, Section 7.2, General Study Procedures List of analytes, Footnote	Add ***** Only applicable for AMG 404 infusion** **ACTH = Adrenocorticotropic hormone; ANA = Antinuclear Antibodies; ANCA = Antineutrophil cytoplasmic antibodies;**
P102, Section 7.2.1 Pre-screening and Screening	Delete ~~The tissue sample must be obtained after last systemic or radiation therapy.~~
P102, Section 7.2.1 Pre-screening and Screening	Replace [redacted] With [redacted]
P102, Investigational In-Vitro Diagnostic Device (IVD)	Add [redacted]
P103, Investigational In-Vitro Diagnostic Device (IVD)	Replace Section 7.1, Table 5, Table 6, Table 7, Table 8, Table 9, and Table 10). With Section 7.1, Table 6, Table 7, Table 8, Table 9, Table 10**, Table 11, Table 12,Table 13, Table 14,Table 15, and Table 16).**
P104, Investigational In-Vitro Diagnostic Device (IVD)	Delete ~~AMG 596 PK collection~~

Section	Amended text
P104, Section 7.2.2 Treatment	Replace Subjects will be hospitalized for the first 7 days of infusion and for at least 24 hours following completion of infusion in cycle 1 and for 72 hours after a dose step in cycle 1, and at least for the first 72 hours in any subsequent cycle and after a dose step in any subsequent cycle. With **All** subjects will be hospitalized for **the following periods:** **Cycle 1:** • **For the first [redacted] of AMG 596 monotherapy (Arm 1)** • **For the first [redacted] of AMG 596 in combination with AMG 404 (Arm 2), hence AMG 404 will be administered on [redacted]** • **For at least 24 hours following completion of AMG 596 cycle 1 for both Arm 1 and Arm 2** • **For additional 72 hours after AMG 596 step dose if necessary** **Cycle 2 and all subsequent cycles:** • **For at least the first 72 hours of AMG 596 infusion in both Arm 1 and Arm 2** • **For additional 72 hours after AMG 596 step dose if necessary.** **Hospitalization may be shortened to 48 hours from the 6th cycle onwards at the discretion of the investigator.** **AMG 404 can be administered in an outpatient setting starting from cycle 1 [redacted] onwards. Subjects should be monitored intensely in hospital or outpatient clinic for at least 4 hours after start of each AMG 404 infusion from cycle 1 [redacted] onwards.**
P105, Section 7.2.2 Treatment	Replace Dosing with AMG 596 can continue unless the subject becomes intolerant to investigational product, With Dosing with AMG 596 **or AMG 596 in combination with AMG 404** can continue unless the subject becomes intolerant to investigational product,

Section	Amended text
P106, Section 7.2.2 Treatment	Replace Biomarker assessments: [redacted] With Biomarker assessments: [redacted]
P106, Section 7.2.2 Treatment	Replace [redacted] With [redacted]
P107, Section 7.2.4, Safety Follow Up Visit	Replace The safety follow-up visit (SFUP) is to be performed 30 days (+/- 7 days) after the last dose of AMG 596 or prior to the initiation of other therapy With The safety follow-up visit (SFUP) is to be performed 30 days (+/- 7 days) after the last dose of AMG 596 **and AMG 404 even if the subject begins another therapy.**
P107, Section 7.2.4, Safety Follow Up Visit	Replace [redacted] With [redacted]
P111, Section 7.3.10 Physical Examination	Add **Table 12, Table 13, Table 14,Table 15, and Table 16**
P111, Section 7.3.12, Clinical Laboratory Test	Add **Table 12, Table 13, Table 14,Table 15, and Table 16**

Section	Amended text
P112, Section 7.4 Pharmacokinetic Blood Sampling	Replace Blood samples will be obtained for determination of serum concentrations of AMG 596 at the time points specified in the Schedules of Assessments (section 7.1, Table 5, Table 6, Table 7, Table 8, Table 9 and Table 10). Blood must not be drawn from the port catheter. With Blood samples will be obtained for determination of serum concentrations of AMG 596 **in the monotherapy and for the determination of serum concentrations of AMG 596 and AMG 404 in the combination therapy** at the time points specified in the Schedules of Assessments **(section 7.1, Table 6, Table 7, Table 8, Table 9, Table 10, table 11, table 12 and table 13).**
[redacted]	Replace [redacted] With [redacted]

Section	Amended text
[redacted]	Add [redacted]
P114, Section 7.8, Sample Storage and Destruction	Replace the dose response and/or prediction of response to AMG 596 With the dose response and/or prediction of response to AMG 596 **and in combination with AMG 404**
P118, Section 9.1.1, Disease Related Events, Table 15	Replace Table 12, Disease-Related Adverse Events by System organ Class With **Table 18**, Disease-Related Adverse Events by System organ Class
P120, Section 9.1.3 Serious Adverse Events	Delete • ~~the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or~~ • ~~if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event~~
P120, Section 9.2.1 Reporting Procedures for Disease Related Events	Delete ~~Disease-Related Events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/ study treatment/ protocol-required therapies, and determined to be serious, must be recorded on the Event eCRF as Serious Adverse Events.~~

Section	Amended text
P120, Section 9.2.1 Reporting Procedures for Disease Related Events	Add **All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease-related event data to the sponsor within 24 hours of it being available.** **Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events and recorded and reported per section 9.2.1 and Appendix J.** **Disease-related events pre-defined for this study are listed in Table 18.**
P123, Section 9.3 Pregnancy and Lactation Reporting	Replace In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 30 days after the last dose of protocol-required therapies. With In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur through 30 days after the last dose **of AMG 596 or through 4 months (120 days) after the last dose of AMG 404.**
P124, Section 10.1.1 Secondary Endpoint	Add **PK parameters of AMG 404 including, but not limited to, maximum observed serum concentration (C_{max}), time to achieve C_{max} (t_{max}), and AUC** **PK parameters for AMG 596 dosed in combination with AMG 404 including, but not limited to, average steady-state concentration (C_{ss}), area under the concentration-time curve (AUC), clearance, volume of distribution and half-life (t1/2) for serum AMG 596.**
P124, Section 10.1.1 Study Endpoints, Secondary Endpoint	Replace Objective response (OR) as per modified RANO, time to response, response duration and time to progression (TTP); progression free survival (PFS) at 6 and 12 months after treatment initiation. With Objective response (OR) as per modified RANO, time to response, response duration and time to progression (TTP); progression free survival (PFS) at 6 and 12 months after treatment initiation **with AMG 596 monotherapy or AMG 596 in combination with AMG 404.**

Section	Amended text
P124, Section 10.1.1, Study Endpoints, Exploratory Endpoints	Replace [redacted] With [redacted]F
P124, Section 10.1.1, Study Endpoints, Exploratory Endpoints	Replace [redacted] With [redacted]
P124, Section 10.1.1, Study Endpoints, Exploratory Endpoints	Replace [redacted] With [redacted]
P124, Section 10.1.2 Analysis Sets	Add **RANO Evaluable Analysis Set** **The RANO Evaluable Analysis Set includes all subjects that are enrolled and receive at least one administration of AMG 596 with measurable disease at enrollment per RANO.**
P124, Section 10.1.2 Analysis sets	Replace The DLT Evaluable Analysis Set will be used to summarize incidence of dose limiting toxicity (DLT) (see Section 3.3. for definition of DLT-evaluable) With The DLT Evaluable Analysis Set **includes subjects who are DLT-evaluable and** will be used to summarize incidence of dose limiting toxicity (DLT) (see Section 3.3. for definition of DLT-evaluable)
P126, Section 10.2, Sample Size Considerations	Delete ~~It is anticipated that around 82 subjects will be enrolled in the study. Up to 30 DLT-evaluable subjects will be enrolled in dose escalation Group 1 (recurrent disease) and up to 12 subjects in dose escalation Group 2 (maintenance setting). Up to 40 subjects will be enrolled in the dose expansion cohorts (15 subjects in Group 1 and up to 25 subjects in Group 2) at 9 or more sites across US, Australia and Europe.~~

Section	Amended text
P126, Section 10.2, Sample Size Considerations	Add **It is anticipated that up to 190 subjects** will be enrolled in the study**. It is anticipated that up to 100 subjects will be enrolled to Arm 1 in this study and up to 90 subjects will be enrolled to Arm 2 in this study.** **For Group 1 (recurrent disease), the following are the planned sample sizes.** • **In dose escalation, up to 45 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 30 DLT-evaluable subjects to combination Arm 2** • **In dose expansion, up to 15 subjects will be enrolled to monotherapy Arm 1 and up to 15 subjects to combination Arm 2** **For Group 2 (maintenance setting), the following are the planned sample sizes.** • **In dose escalation, up to 15 DLT-evaluable subjects will be enrolled to monotherapy Arm 1 and up to 20 DLT-evaluable subjects to combination Arm 2** • **In dose expansion, up to 25 subjects will be enrolled to monotherapy Arm 1 and up to 25 subjects to combination Arm 2**
P126, Section 10.2, Sample Size Considerations	Replace The sample size of dose expansion Group 1 is based on practical considerations. With 21 subjects treated at the Group 1RP2D/MTD (6 from dose escalation and 15 from dose expansion) With **For Group 1 (recurrent disease) in each respective arm (monotherapy and combination), the respective** sample sizes of the dose expansion cohorts are based on practical considerations. With 21 subjects treated at the RP2D/MTD (6 from dose escalation and 15 from dose expansion) **in an arm**
P126, Section 10.2, Sample Size Considerations	Replace The sample size for Group 2 dose expansion is based on a Bayesian predictive probability design (Lee, 2008). In Group 2, the ORR of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. With **For Group 2 (maintenance setting) in each respective arm (monotherapy and combination),** the sample sizes in the respective dose expansion arm are based on a Bayesian predictive probability design (Lee, 2008). **For both arms,** the ORR of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity.

Section	Amended text
P126, Section 10.2, Sample Size Considerations	Replace In Group 2, the ORR of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. The maximum sample size is 31 subjects (6 from dose escalation and 25 from dose expansion). With **For both arms**, the ORR of interest is 20% or higher while an ORR of 5% or less is considered insufficient antitumor-activity. The maximum sample size **per arm** is 31 subjects (6 from dose escalation and 25 from dose expansion).
P126, Section 10.2 Sample Size Consideration,	Add **During dose expansion and separately for the monotherapy arm (combining data from groups 1 and 2) and for the combination arm (combining data from groups 1 and 2),**

<table>
<tr><th>Section</th><th>Amended text</th></tr>
<tr><td>P128, Table 19</td><td>
Replace
Table 13a, Stopping Boundary for Dose Expansion with Posterior Probability of 80% and Grade 4 or Higher Treatment-Related Adverse Event Limit of 20%
<table>
<tr><th>Number of subjects</th><th>Hold enrollment if observing this many grade 4 or higher treatment-related adverse events</th></tr>
<tr><td>10</td><td>≥ 4</td></tr>
<tr><td>20</td><td>≥ 6</td></tr>
<tr><td>30</td><td>≥ 9</td></tr>
<tr><td>35</td><td>Study Complete</td></tr>
</table>
With
Table 19. Stopping Boundary for Dose Expansion with Posterior Probability of 80% and Grade 4 or Higher Treatment-Related Adverse Event Limit of 20%
<table>
<tr><th>Number of subjects</th><th>Hold enrollment if observing this many grade 4 or higher treatment-related adverse events</th></tr>
<tr><td>10</td><td>≥ 4</td></tr>
<tr><td>20</td><td>≥ 6</td></tr>
<tr><td>30</td><td>≥ 9</td></tr>
<tr><td>40</td><td>Study Complete</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td>Section</td><td>Amended text</td></tr>
<tr><td>P128, Table 20</td><td>Replace
<table>
<tr><th>True grade 4 or higher treatment-related adverse event rate</th><th>Probability of early stopping of dose expansion</th><th>Average dose expansion sample size</th></tr>
<tr><td>0.10</td><td>2.1%</td><td>34.6</td></tr>
<tr><td>0.15</td><td>9.7%</td><td>33.1</td></tr>
<tr><td>0.20</td><td>25.8%</td><td>30.2</td></tr>
<tr><td>0.25</td><td>47.7%</td><td>26.2</td></tr>
<tr><td>0.30</td><td>69.2%</td><td>21.9</td></tr>
</table>
With
Table 20. Operating Characteristics with Batch Size of 10 Subjects
<table>
<tr><th>True grade 4 or higher treatment-related adverse event rate</th><th>Probability of early stopping of dose expansion</th><th>Average dose expansion sample size</th></tr>
<tr><td>0.10</td><td>2.0%</td><td>39.5</td></tr>
<tr><td>0.15</td><td>9.7%</td><td>37.6</td></tr>
<tr><td>0.20</td><td>25.8%</td><td>33.9</td></tr>
<tr><td>0.25</td><td>47.7%</td><td>28.8</td></tr>
<tr><td>0.30</td><td>69.2%</td><td>23.4</td></tr>
</table></td></tr>
</table>

Section	Amended text
P128, Section 10.3 Adaptive Design	Add **During dose escalation for both Arm 1 and Arm 2**,
P129, Section 10.3 Adaptive Design	Replace A bi-variate normal prior distribution (Neuenschwander, Branson and Gsponer; 2008) is used to select for θ = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at the lowest planned dose ([redacted] µg/day) is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose ([redacted] µg/day) is 0.05. With **For both Arm 1 and Arm 2 ,** a bi-variate normal prior distribution (Neuenschwander, Branson and Gsponer; 2008) is used to select for θ = (log a, log b) where the probability that the true DLT rate is ≤ 0.40 at the lowest **monotherapy** planned dose ([redacted] µg/day) is 0.90 and the probability the true DLT rate is ≤ 0.05 at the reference dose ([redacted] µg/day) is 0.05.
P129, Section 10.4.1 Interim Analysis	Add **Arm 1**
P129, Section 10.4.1 Interim Analysis	Add **Arm 2** **In dose escalation, the DLRT will review the safety data after each cohort and make a decision on the next dose level to be explored for the estimate of RP2D/MTD based on a BLRM design. The RP2D/MTD will be established separately for Group 1 (recurrent disease) and Group 2 (maintenance setting) subjects.** **Interim safety analyses during dose expansion will occur once 1) 5 subjects with recurrent disease have been enrolled and 2) after enrollment of 10 subjects with maintenance setting. The BLRM will estimate the RP2D/MTD using available data from dose escalation and dose expansion. Based on this revised RP2D/MTD estimate and reviewing all available safety data, the dose level for dose expansion may be revised. In Part 2 dose expansion, the ORR will be evaluated after treating n=10 Group 2 subjects for at least 6 months. The futility will be assessed initially for N=10 and continuously afterwards using a Bayesian predictive probability design. Enrollment may be terminated if insufficient antitumor-activity is observed.**

Section	Amended text
P131, Section 10.5.1 General Considerations	Add: **The analyses described below will be reported separately for subjects enrolled to Arm 1 and for subjects enrolled to Arm 2. Unless otherwise specified, the analyses will be done using the Safety Analysis Set.**
P131, Section 10.5.1 General Considerations	Replace ORR will be presented with 80% Clopper-Pearson exact CI. With ORR will be presented with 80% Clopper-Pearson exact CI **using the RANO Evaluable Analysis Set.**
P131, Section 10.5.2 Dose Limiting Toxicities (DLT)	Add **The DLT endpoint will be analyzed using the DLT Evaluable Analysis Set.**
P132, Section 10.5.3 Secondary Endpoint	Replace An exact 80% CI will be estimated for the OR rate for all subjects in part 2 and those in part 1 treated at RP2D/MTD for each group. With **Using the RANO Evaluable Analysis Set,** an exact 80% CI will be estimated for the OR rate for all subjects in part 2 and those in part 1 treated at RP2D/MTD for each group.

Section	Amended text
P131, Section 10.5, Planned Method of Analysis, Secondary Endpoints, Pharmacokinetic Analyses	Replace The serum PK parameters of AMG 596 including, but not limited to, average C_{ss}, area under the concentration-time curve (AUC), clearance, volume of distribution and half-life ($t_{1/2}$), [redacted] CSF will be estimated using non-compartmental methods and summarized by dose level using means, standard deviations, medians, minimums, and maximums. With The serum PK parameters of AMG 596 **as monotherapy or in combination therapy with AMG 404** including, but not limited to, average C_{ss}, area under the concentration-time curve (AUC), clearance, volume of distribution, half-life ($t_{1/2}$), and [redacted] **and serum PK parameters of AMG 404 including, but not limited to, C_{max}, t_{max}, and AUC** will be estimated using non-compartmental methods and summarized by dose level using means, standard deviations, medians, minimums, and maximums.
P131, Section 10.5. Planned Method of Analysis Exploratory Endpoint	Replace [redacted] With [redacted]
P131, Section 10.5, Planned Method of Analysis, Exploratory Endpoint	Delete [redacted]
P140, Reference	Add **AMG 404 Investigator's Brochure. Thousand Oaks, CA: Amgen Inc.**

Section	Amended text
P140, Reference	Add **Berghoff AS, Kiesel B, Widhalm G, Rajky O, Ricken G, Wöhrer A, Dieckmann K, Filipits M, Brandstetter A, Weller M, Kurscheid S, Hegi ME, Zielinski CC, Marosi C, Hainfellner JA, Preusser M, Wick W. Programmed death ligand 1 expression and tumor-infiltrating lymphocytes in glioblastoma. *Neuro Oncology*. 2015 Aug;17(8):1064-75.**
P140, Reference	Add **Cloughesy TF, Mochizuki AY, Orpilla JR, Hugo W, Lee AH, Davidson TB, Wang AC, Ellingson BM, Rytlewski JA, Sanders CM, Kawaguchi ES, Du L, Li G, Yong WH Gaffey SC, Cohen AL, Mellinghoff IK, Lee EQ, Reardon DA, O'Brien BJ, Butowski NA, Nghiemphu PL, Clarke JL, Arrillaga-Romany IC, Colman H, Kaley TJ, de Groot JF, Liau LM, Wen PY, Prins RM. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma*. *Nat Med.* **2019 Mar;25(3):477-486.**
P141, Reference	Add **Kufer P, Kischel R, Zugmaier G, Lichtenegger FS, Kohnke T, Vick B, Jeremias I, Metzeler KH, Altmann T, Schneider S, Fiegl M, Spiekermann K, Bauerle PA, Hiddemann W, Riethmüller G, Subklewe M. Blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: reversing a T-cell-induced immune escape mechanism. *Leukemia* (2016) 30:484–91.**
P141, Reference	Add **Omuro, A. , Vlahovic, G., Lim,M., Sahebjam,S., Baehring, J.,, Cloughesy, T.,, Voloschin, A., Ramkissoon, S.H., Ligon, K.L.,Latek,R. ,Zwirtes, R. Strauss,L., Paliwal, P., Harbison, C.T., Reardon, D.A.,Sampson, J.H.,Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: results from exploratory phase I cohorts of CheckMate 143. *Neuro Oncol*. 2018;20(5):674-686**
P142, Reference	Add **Osada T, Patel SP, Hammond SA, Osada K, Morse MA, Lyerly HK.CEA/CD3-bispecific T cell-engaging (BiTE) antibody-mediated T lymphocyte cytotoxicity maximized by inhibition of both PD1 and PD-L1. *Cancer Immunol Immunother*. (2015) 64:677–88.**

Section	Amended text
P142, Reference	Add **Reardon, D.A., Omuro, A., Brandes, A.A., Rieger, J., Wick,A., Sepulveda,J., Phuphanich,S., de Souza, P., Ahluwalia, M.S., Lim,M., Vlahovic, G., Sampson, J., et al., 2017a. OS10.3: randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. *Neuro Oncol.* 2017 V19 Page iii21**
P142, Reference	Add **Reardon, D.A, Kim, T.,Frenel, J.S.,Santoro, A., Lopez, J., Subramaniam, D.S., Siu, L.L.,Rodon,J., Tamura, K.,Saraf, S., Morosky, A., Stein, K., Soria, J.C., ATIM-35. Results of the phase Ib Keynote-028 multi-cohort trial of pembrolizumab monotherapy in patients with recurrent PD-L1 positive Glioblastoma Multiforme (GBM), *Neuro Oncology*. 2016 V18, P25-26**
P142, Reference	Add **Reardon, D. A., Nayak, L., Peters, K.B., Clarke, J.L., Jordan, J. T., Groot, J. F., Nghiemphe, P. L., Kaley, T. J., Colman,H., Gaffey, S.C., Caruso, V., Debruyne, M. B., Bahavsar, C., Molinaro, A. M., Smith, T., Severgnini, M., Wen, P. Y., Phase II study of pembrolizumab or pembrolizumab plus bevacizumab for recurrent glioblastoma (rGBM) patients. *Journal of Clinical Oncology*, 2018, 36, no. 15_suppl (May 20 2018) 2006-2006**
P142, Reference	Add **Schalper KA, Rodriguez-Ruiz ME, Diez-Valle R, López-Janeiro A, Porciuncula A, Idoate MA, Inogés S, de Andrea C, López-Diaz de Cerio A, Tejada S, Berraondo P, Villarroel-Espindola F, Choi J, Gúrpide A, Giraldez M, Goicoechea I Gallego Perez-Larraya J, Sanmamed MF, Perez-Gracia JL, Melero I. Neoadjuvant nivolumab modifies the tumor immune microenvironment in resectable glioblastoma.*Nat Med*. 2019 Mar;25(3):470-476**
P142, Reference	Add **Wang, X.,Guo, G.,Guan, H.,Yu, Y.,Lu, J., and Yu, J. Challenges and potential of PD-1/PD-L1 checkpoint blockade immunotherapy for glioblastoma.*J Exp Clin Cancer Res.* 2019;38(1) 87. doi: 10.1186/s13046-019-1085-3.**

Section	Amended text
P143, Reference	Add **Zhao J, Chen AX, Gartrell RD, Silverman AM, Aparicio L, Chu T, Bordbar D, Shan D, Samanamud J, Mahajan A, Filip I, Orenbuch R, Goetz M, Yamaguchi JT, Cloney M, Horbinski C, Lukas RV, Raizer J, Rae AI, Yuan J, Canoll P, Bruce JN, Saenger YM, Sims P, Iwamoto FM, Sonabend AM, Rabadan R "Immune and genomic correlates of response to anti-PD-1 immunotherapy in glioblastoma. *Nat Med*. 2019; 25(3):462-469.**
P144, Section 14, Appendices	Replace specified in Section 6.4.2. and Section 6.4.3. With specified in **Section 6.3.3, Section 6.3.4, Section 6.3.5 and Section 6.3.6**
P155, Table 18	Replace Table 13. Measurement Summary With Table **21**. Measurement Summary
P155, Table 19	Replace Table 14. Response Assessment With **Table** 22**. Response Assessment**
P157, Appendix E	Delete ~~Table 15. Grading and Management of Cytokine Release Syndrome (CRS)~~

<table>
<tr><td>Section</td><td>Amended text</td></tr>
<tr><td>P157, Appendix E</td><td>Replace
<table>
<tr><th>CRS Grade</th><th>Description of Severity[a]</th><th>Minimum Expected Intervention</th><th>Instructions for Interruption of AMG 596</th></tr>
<tr><td>1</td><td>Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea,
fatigue, headache, myalgias, malaise</td><td>Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever).
Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier.</td><td>N/A</td></tr>
<tr><td>2</td><td>Symptoms require and respond to moderate intervention
Oxygen requirement
< 40%, OR
Hypotension responsive to fluids or low dose of one
vasopressor, OR
Grade 2 organ toxicity
or grade 3 transaminitis per
CTCAE criteria</td><td>Administer:
Symptomatic treatment (eg, paracetamol/ acetaminophen for fever)
Supplemental oxygen when oxygen saturation is < 90% on room air
Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg > 120 bpm)
may also indicate the need for intervention for hypotension.
Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier.
For subjects with extensive
co-morbidities or poor performance status, manage per grade 3 CRS guidance below.</td><td>Immediately interrupt AMG 596 until event resolves to CRS grade ≤ 1 but for no less than 72 hours.
Permanently discontinue
AMG 596 if there is no improvement to CRS ≤ grade 1 within 7 days.</td></tr>
</table></td></tr>
</table>

Section	Amended text

With

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of **Dosing**
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise	Administer symptomatic treatment (eg, paracetamol/ acetaminophen for fever). Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution, whichever is earlier.	N/A
2	Symptoms require and respond to moderate intervention Oxygen requirement < 40%, OR Hypotension responsive to fluids or low dose of one vasopressor, OR Grade 2 organ toxicity or grade 3 transaminitis per CTCAE criteria	Administer: Symptomatic treatment (eg, paracetamol/ acetaminophen for fever) Supplemental oxygen when oxygen saturation is < 90% on room air Intravenous fluids or low dose vasopressor for hypotension when systolic blood pressure is < 85 mmHg. Persistent tachycardia (eg > 120 bpm) may also indicate the need for intervention for hypotension. Monitor for CRS symptoms including vital signs and pulse oximetry at least Q2 hours for 12 hours or until resolution to CRS grade ≤ 1, whichever is earlier. For subjects with extensive co-morbidities or poor performance status, manage per grade 3 CRS guidance below.	Immediately interrupt **dosing** until event resolves to CRS grade ≤ 1 but for no less than 72 hours. Permanently discontinue AMG 596 and **AMG 404** if there is no improvement to CRS ≤ grade 1 within 7 days.

Section	Amended text
P164, Appendix E	Replace

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of AMG 596
3	Symptoms require and respond to aggressive Intervention Oxygen requirement ≥ 40%, OR Hypotension requiring high dose[b] or multiple vasopressors, OR Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise. Investigators may also consider use of Tocilizumab as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose.	Immediately interrupt AMG 596 until event resolves to CRS grade ≤ 1 but for no less than 72 hours. Permanently discontinue AMG 596 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days.
4	Life-threatening symptoms requirement for ventilator support OR Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, Tocilizumab can be considered administered at a dose of 4-8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	Immediately stop the infusion and permanently discontinue AMG 596 therapy.

Section	Amended text

With

CRS Grade	Description of Severity[a]	Minimum Expected Intervention	Instructions for Interruption of **Dosing**
3	Symptoms require and respond to aggressive Intervention Oxygen requirement ≥ 40%, OR Hypotension requiring high dose[b] or multiple vasopressors, OR Grade 3 organ toxicity or grade 4 transaminitis per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). The dose should then be reduced step-wise. Investigators may also consider use of Tocilizumab as an additional therapy in this setting at a dose of 4-8 mg/kg as a single dose.	Immediately interrupt **dosing** until event resolves to CRS grade ≤ 1 but for no less than 72 hours. Permanently discontinue AMG 596 if there is no improvement to CRS ≤ grade 2 within 5 days or CRS ≤ grade 1 within 7 days.
4	Life-threatening symptoms requirement for ventilator support OR Grade 4 organ toxicity (excluding transaminitis) per CTCAE criteria	Admit to intensive care unit for close clinical and vital sign monitoring per institutional guidelines. Administer dexamethasone (or equivalent) IV at a dose maximum of 3 doses of 8 mg (24 mg/day). Further corticosteroid use should be discussed with the Amgen medical monitor. Additionally, Tocilizumab can be considered administered at a dose of 4-8 mg/kg as a single dose and may be repeated once within 24 to 48 hours based on clinical assessment.	Immediately stop the infusion and permanently discontinue AMG 596 and **AMG 404** therapy.

<table>
<tr><td>Section</td><td>Amended text</td></tr>
<tr><td>160-167, Appendix G</td><td>Add
Appendix H. Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Reactions Associated with AMG 404*</td></tr>
<tr><td>P168, Appendix H</td><td>Add
Appendix I. Management of Infusion Related Reactions with AMG 404
<table>
<tr><th>Severity (CTCAE Grade Version 5.0)</th><th>AMG 404 Dose Modification</th><th>Management</th><th>Premedication at Subsequent Dosing</th></tr>
<tr><td>Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)</td><td>Interrupt or slow the rate of the infusion.</td><td>• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.
• Treat per institutional guidelines.</td><td>None</td></tr>
<tr><td>Grade 2 (therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours)</td><td>Interrupt or slow the rate of the infusion. For subjects who develop grade 2 infusion-related reaction despite adequate premedication, permanently discontinue AMG 404.</td><td>• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.
• Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, and narcotics.</td><td>Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of AMG 404 with:
• Diphenhydramine 50 mg orally (or equivalent dose of antihistamine).
• Acetaminophen 500-1000 mg orally (or equivalent dose of antipyretic).</td></tr>
<tr><td>Grade 3 (prolonged [e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae)
OR
Grade 4 (life-threatening consequences; urgent intervention indicated)</td><td>Permanently discontinue study drug.</td><td>• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable.
• Hospitalization may be indicated.
• Treat per institutional guidelines. Additional appropriate medical therapy may include but is not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids, and epinephrine. In cases of anaphylaxis, epinephrine should be used immediately.</td><td>No subsequent dosing</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Section</td><td>Amended text</td></tr>
<tr><td>P169, Appendix I</td><td>Add

Appendix J, Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

<table><tr><th>Disease-related Event Definition</th></tr><tr><td>• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See [Section 9.2.3.1.1.1 / Section 12.8] for the list of disease-related events. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.
• Disease-related events that would qualify as an adverse event or serious adverse event:
○ An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject’s condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
○ An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.</td></tr></table></td></tr>
</table>

Amendment 4

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 in Subjects With Glioblastoma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Amgen Protocol Number 20160132

IND Number 134352

EudraCT number 2017-001658-32

Amendment Date: 11 March 2019

Rationale:

Protocol Amendment 4 includes changes to allow enrollment of a broader patient population and allow treatment with potentially efficacious doses as early as possible.

Revisions to Protocol Amendment 4 include:

- Update the treatment schema to reflect the switch in Cohort 2 to a [redacted] continuous infusion treatment cycle and multiple subject cohorts
- Allow intrasubject dose escalation to minimize the number of subjects receiving sub-therapeutic doses
- Allow for up to 5 subjects to be enrolled into a cohort. On a limited basis, one additional subject may be allowed to be enrolled if the subject has been determined to be eligible and the cohort has been filled.
- Allow subjects with lower grade malignant gliomas that are EGFRvIII positive to be enrolled
- Align treatment discontinuation with Dose Limiting Toxicities
- Add stopping rules for dose expansion.

In addition, clarifications and corrections of inconsistencies, and administrative and typographical changes were made throughout the protocol.

Amendment 3

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 in Subjects With Glioblastoma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Amgen Protocol Number 20160132

IND Number 134352

EudraCT number 2017-001658-32

Amendment Date: 17 May 2018

Rationale:

The protocol amendment #3 is amended to provide additional information on [redacted]. The plasma test is due to be available in the second half of 2018 and will be used in place of having subjects undergo a repeat surgery or biopsy to confirm EGFRvIII positivity. The current biopsy requirement is not feasible in patients with advanced glioblastoma and rapid deterioration, as there is too much time required for the procedure and obtaining results using the biopsy confirmation. Therefore, the protocol is being revised to allow:

- Enrollment of subjects based on testing of available tumor tissue until availability of the plasma-based test. Testing prior to enrollment is required for subjects who received an EGFRvIII or amplified EGFR targeting therapy. Plasma will be collected from all subjects prior to treatment start allowing retrospective testing for EGFRvIII.
- A short description of the plasma-based test will be added
- Validated local tests for EGFRvIII detection will be allowed for pre-screening

This revised approach for EGFRvIII positive glioblastoma identification can be justified as it is known that EGFRvIII expression is very heterogeneous. In particular, tests based on a small tissue sample derived from a biopsy may not reflect the expression status in other tumor areas. Quantitative differences for EGFRvIII detection between primary and recurrent glioblastomas are reported in up to 50% of cases though, qualitative differences were much lower with EGFRvIII expression remaining similar in 79% (Bent et al, 2015) and 87.5% (Felsberg et al, 2017) of glioblastomas. Loss of EGFRvIII expression was described as a potential resistance mechanism in glioblastomas treated with an EGFRvIII targeting vaccine, rindopepimut. In consequence, the request for

EGFRvIII testing on tissue obtained shortly before or during screening remains in the protocol for subjects treated with EGFRvIII- or the amplified EGF receptor targeting agents (Schuster et al, 2015).

Van den Bent et al: Neuro Oncol. 2015 Jul;17(7):935-41.

Schuster et al, Neuro Oncol. 2015 Jun;17(6):854-61.

Felsberg et al. *Clin Cancer Res, 23*(22), 6846-6855.

In addition, few clarifications or corrections of inconsistencies, administrative and typographical changes were made throughout the protocol.

Amendment 2

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 in Subjects With Glioblastoma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Amgen Protocol Number 20160132

IND Number 134352

EudraCT number 2017-001658-32

Amendment Date: 30 January 2018

Rationale:

The protocol amendment #2 addresses several comments and changes requested by either European Ethics Committees or Regulatory Authorities based on Protocol Amendment #1.

In addition to clarifications or corrections of inconsistencies, administrative and typographical changes were made throughout the protocol.

Amendment 1

Protocol Title: Phase 1 Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of AMG 596 in Subjects With Glioblastoma Expressing Mutant Epidermal Growth Factor Receptor Variant III (EGFRvIII)

Amgen Protocol Number 20160132

IND Number 134352

EudraCT number 2017-001658-32

Amendment Date: Draft 05 July 2017

Rationale:

Protocol is amended to incorporate FDA recommendations based on review of the IND and recommendations of the Melbourne Health Human Research Ethics Committee from the meeting on 14/06/2017.

Also administrative, typographical and formatting changes were made throughout the protocol.