2. SYNOPSIS

Name of Sponsor: Amgen, Inc.

Name of Finished Product: To be determined

Name of Active Ingredient: AMG 780

Title of Study: A Phase 1, First-in-Human Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AMG 780 in Adult Subjects With Advanced Solid Tumors

Investigators and Study Centers: This study was conducted at 3 centers in the United States. Centers and principal investigators are listed in Section 16.1.4.

Publications: None.

Study Period: The first subject was enrolled on 03 August 2010. The last subject completed follow-up on 17 December 2013.

Development Phase: 1

Objectives:

Primary

- to assess the safety and tolerability
- to evaluate the pharmacokinetics (PK)

Secondary

- to evaluate tumor response using response evaluation criteria in solid tumors (RECIST) criteria (measured by computed tomography [CT]/magnetic resonance imaging [MRI])
- to evaluate changes in tumor volume (measured by volumetric CT/MRI)
- to evaluate changes in tumor vascularity and to estimate the relationship between dose/PK and vascular response (measured by dynamic contrast-enhanced magnetic resonance imaging [DCE-MRI])
- to evaluate incidence of anti-AMG 780 antibody formation

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Methodology:

This was a first-in-human (FIH), open-label, sequential dose-escalation study evaluating AMG 780 in subjects with advanced solid tumors. This study was planned to be conducted in 2 parts: dose escalation and dose expansion.

The dose escalation part of the study aimed to determine the maximum tolerated dose (MTD), if feasible, and to evaluate the safety, tolerability, PK, and PD of AMG 780. It consisted of 9 cohorts of 3 to 10 subjects each at doses of 0.1, 0.3, 0.6, 1.2, 2.5, 5, 10, 20, and 30 mg/kg. Dose-escalation decisions were to be made in accordance with a standard 3+3 design as

described in the protocol. Dose escalation was to occur at the planned dose levels until the MTD was determined or until the highest dose level was tested. Subjects enrolled in the dose escalation phase of the study received an AMG 780 intravenous (IV) infusion every 2 weeks (Q2W) for 4 doses (at week 1, 3, 5, and 7) beginning at study day 1. Treatment IV Q2W could resume at week 10 unless there was radiographic evidence of progressive disease per RECIST (at week 9), the subject became intolerant to the investigational product, or signs and symptoms of clinical progression were evident as determined by the investigator. Further details on dose escalation are provided in Protocol Section 3.1 (Section 16.1.1 of this report).

The dose expansion phase was planned to further characterize the AMG 780 safety and PK profile and the relationship between dose/PK and vascular response (as measured by DCE-MRI). However, an MTD for AMG 780 was not determined; the highest dose tested was 30 mg/kg IV Q2W. The planned dose expansion phase of the study was not conducted due to a business decision.

Number of Subjects Planned: Up to 65 subjects.

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women ≥ 18 years old with a pathologically documented, and definitively diagnosed, advanced solid tumor measurable by RECIST criteria. Disease was to be refractory to standard treatment, or have no curative therapy available, or subjects were to have refused standard therapy. Eligible subjects had Eastern Cooperative Oncology Group performance status ≤ 2 and a life expectancy of > 3 months. Subjects had to be eligible to undergo MRI evaluation.

The complete list of eligibility criteria is provided in Protocol Section 4 (Section 16.1.1 of this report).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Each glass vial contained 1 mL deliverable volume of AMG 780 with a concentration of 70 mg/mL. The AMG 780 preparations were administered Q2W by IV infusion.

Nine dose levels were planned to be tested in the dose escalation part of this study.

Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

No placebo or active comparator was used in this study.

Duration of Treatment:

The duration of this study was anticipated to be approximately 24 months, with about 15 months of enrollment period and 9 months protocol treatment period. In the event that subjects demonstrated a persistent clinically favorable response accompanied by a documented radiographic response after 4 doses of AMG 780 (complete or partial response, or stable disease as defined by RECIST), subjects could continue treatment with AMG 780 until they experienced an unacceptable adverse event or disease progression or withdrew consent.

Study Endpoints:

Primary Endpoints

- Safety: subject incidences of dose limiting toxicities (DLTs) and adverse events, and clinically significant changes in vital signs, electrocardiograms, and clinical laboratory tests
- AMG 780 PK parameters including, but not limited to, maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), area under the serum concentration-time curve (AUC) after first and fourth dose, and accumulation ratio after 4 doses

Secondary Endpoints

- tumor response measured by CT or MRI and assessed per RECIST criteria
- changes in tumor volume measured by volumetric CT or MRI

- subject incidence of anti-AMG 780 antibody formation
- change in tumor vascularity (volume transfer coefficient [K^{trans}] and initial area under the time-concentration curve [IAUC], measured by DCE-MRI) from baseline to week 5

Statistical Methods:

Standard PK parameters were estimated using noncompartmental analysis. Descriptive statistics were provided for selected demographic, safety, PK, and imaging data by dose and time as appropriate. Descriptive statistics on continuous data included means, medians, standard deviations (SD), and ranges, while categorical data were summarized using frequency counts and percentages. Graphical summaries of the data were presented.

Summary of Results:

Subject Disposition:

Forty-four subjects of the 45 enrolled received AMG 780 across 9 cohorts at doses ranging from 0.1 to 30 mg/kg IV Q2W and were evaluable for safety and PK analysis (1 subject in the 10-mg/kg dose group withdrew consent before receiving any dose of AMG 780):

- 0.1-mg/kg dose group (3 subjects)
- 0.3-mg/kg dose group (3 subjects)
- 0.6-mg/kg dose group (6 subjects)
- 1.2-mg/kg dose group (3 subjects)
- 2.5-mg/kg dose group (6 subjects)
- 5-mg/kg dose group (3 subjects)
- 10-mg/kg dose group (10 subjects)
- 20-mg/kg dose group (3 subjects)
- 30-mg/kg dose group (8 subjects)

All subjects discontinued AMG 780. Most subjects discontinued due to disease progression (35 subjects). The remaining subjects discontinued due to adverse events (5 subjects), death (1 subject), withdrawal of full consent (1 subject), withdrawal of partial consent (1 subject), and other reasons (2 subjects). Of the 45 enrolled subjects, 29 subjects completed the study and 15 subjects discontinued from the study; 1 subject withdrew full consent before receiving AMG 780 and was not included in the safety analysis set for this study.

Baseline Demographics:

Sex: 43.2% men; 56.8% women

Age (Mean [SD]): 61.0 (9.1) years

Ethnicity/Race: 93.2% white; 2.3% black; 2.3% Hispanic; 2.3% Asian

Pharmacokinetic Results:

Human PK of AMG 780 was evaluated after Q2W administration in subjects with advanced solid tumors. Intensive PK sampling was done after the first and fourth dose only. AMG 780 exhibited linear PK after single-dose administrations over the dose range of 0.1 to 30 mg/kg; the exposure, measured by mean C_{max} and area under the concentration-time curve during the dosing interval (tau) ([AUC_{tau}] with tau equal to 336 hours), increased in a dose proportional manner. Following a single 60-minute IV infusion, C_{max} was predominantly observed at the end of the infusion with median t_{max} equal to 1 hour across doses.

The mean volume of distribution at steady state (V_{ss}) at all dose levels was 31.4 mL/kg. The mean clearance after intravenous administration (CL) for the 2 lower doses, 0.1 and 0.3 mg/kg, were 0.55 and 0.64 mL/hr/kg with high intersubject variability (coefficient of variance [CV%]) of

77% and 56%, respectively. For all other doses tested (0.6 to 30 mg/kg), the estimated mean CL was 0.16 mL/hr/kg. The terminal half-life ($t_{1/2,z}$)for the therapeutic dosing range ($\geq$ 2.5 mg/kg) varied between 8 and 13 days. Steady state was reached after 3 Q2W doses, and mean accumulation ratio was 1.6.

One AMG 780-treated subject tested positive for pre-existing, neutralizing anti-AMG 780 binding antibodies at day 1 at baseline. This subject did not test positive for anti-AMG 780 antibodies at any time points after AMG 780 administration. The presence of neutralizing anti-AMG 780 antibodies in this subject had no effect on serum AMG 780 concentrations.

The mean C_{min} concentrations at 2.5 mg/kg (28.1 μg/mL) exceeded the EC_{50} (1.2 μg/mL) and EC_{90} (10.4 μg/mL) values obtained from xenograft Colo 205 human colon carcinoma model (Study R20070979).

Efficacy Results:

Nine of the 44 subjects who received AMG 780 (1 subject in the 0.6-mg/kg dose group, 1 subject in the 2.5-mg/kg dose group, 5 subjects in the 10-mg/kg dose group, and 2 subjects in the 30-mg/kg dose group) did not have any postbaseline scans and were excluded from the efficacy analysis. Of the 35 evaluable subjects, 8 subjects (1 subject each in the 0.1-, 0.3-, 0.6-, 2.5-, 20-, and 30-mg/kg dose groups and 2 subjects in the 10 mg/kg dose group) had a best overall response of stable disease; the subject in the 0.6 mg/kg dose group had stable disease lasting > 6 months. The remaining 27 of 35 evaluable subjects had progressive disease. Change from baseline in tumor size ranged from a 25% decrease to a 135% increase in the sum of tumor diameters across all treatment cohorts. Decrease in tumor diameter was observed for 1 subject each in the 0.6- and 30-mg/kg dose groups and 2 subjects in the 2.5-mg/kg dose group, and was considered to be the best overall response.

Approximate change from baseline tumor volume ranged from a maximum decrease of 40.7% to a maximum increase of > 500% across the treatment cohorts; a decrease in tumor volume was observed for 1 subject in the 2.5-mg/kg dose group, 2 subjects in the 10-mg/kg dose group, and 1 subject in the 30-mg/kg dose group.

Pharmacodynamic Results:

DCE-MRI Results

The DCE-MRI was conducted in 22 subjects. Sixteen subjects had interpretable complete data from baseline and followup scans, 2 subjects each had 2 evaluable tumors. Data from 5 subjects were not interpretable because of unavailability of week-5 predose and/or postdose scans (n = 4), or inadequate baseline scans (n = 2). Of the 16 subjects with DCE-MRI data, 6 subjects had > 20% reductions in K^{trans} and IAUC at week 5 postdose relative to baseline (K^{trans} for 7 tumors in 6 subjects and IAUC for 6 tumors in 6 subjects); the remaining subjects did not show vascularity effect by AMG 780.

Biomarker Results:

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Anti-AMG 780 Antibody Assays:

A total of 44 subjects (44 subjects with a baseline sample and 33 subjects with a postbaseline sample) were tested for anti-AMG 780 antibodies. No developing antibodies were detected. One of 44 subjects (2.3%) tested positive for pre-existing neutralizing binding antibodies at day 1 baseline.

Safety Results:

Forty-five subjects were enrolled. A total of 44 subjects received ≥ 1 dose of AMG 780 and were included in the safety analysis set. One subject in the 10-mg/kg dose group withdrew consent before receiving AMG 780.

Treatment emergent adverse events were reported for all 44 subjects in the safety analysis set. The most frequent treatment emergent adverse events (occurring in > 20% of subjects) by preferred term were hypoalbuminemia (15 [34.1%] subjects; 9 [20.5%] subjects had a grade ≥ 2 event of which 1 [2.3%] subject had a grade 3 event), peripheral edema (13 [29.5%] subjects; 6 [13.6%] subjects had a grade 2 event), decreased appetite (12 [27.3%] subjects; 3 [6.8%] subjects had a grade 2 event), fatigue (12 [27.3%] subjects; 8 [18.2%] subjects had a grade ≥ 2 event of which 1 [2.3%] subject had a grade 3 event), hyponatremia (9 [20.5%] subjects; 3 [6.8%] subjects had a grade 3 event), lymphopenia (9 [20.5%] subjects; 6 [13.6%] subjects had a grade ≥ 2 event of which 2 [4.5%] subjects had a grade 3 event), and nausea (9 [20.5%] subjects; 2 [4.5%] subjects had a grade 2 event).

Adverse events considered by the investigator to be possibly treatment related were reported for 63.6% of subjects. The most frequent, treatment-related adverse events (occurring in > 10% of subjects) were fatigue (7 [15.9%] subjects; 3 [6.8%] subjects had a grade 2 event), decreased appetite (6 [13.6%] subjects; 1 [2.3%] subject had a grade 2 event), nausea (6 [13.6%] subjects; 1 [2.3%] subject had a grade 2 event), and peripheral edema (6 [13.6%] subjects; 3 [6.8%] subjects had a grade 2 event). All other possible treatment-related adverse events occurred in 4 (9.1%) or fewer subjects each.

A total of 47 adverse events in 16 subjects were recorded as leading to discontinuation of AMG 780. In 6 of these subjects the events were serious (completed suicide; ascites; sepsis; pulmonary embolism; atrial fibrillation and hepatic infection; and pleural effusion and increased aspartate aminotransferase, alkaline phosphatase, and bilirubin). Two of the subjects (1 with pulmonary embolism and 1 with proteinuria) discontinued the study as well as AMG 780 as a result of these events.

A total of 25 serious adverse events were reported in 16 (36.4%) subjects. Serious adverse events that occurred in more than 1 subject each were ascites (2 [4.5%] subjects), dyspnea (2 [4.5%] subjects), and pleural effusion (2 [4.5%] subjects). Only 1 serious adverse event (pericardial effusion) was assessed by the investigator as related to treatment.

Three subjects experienced DLTs during this study:

- One subject in the 0.6-mg/kg dose group had a DLT of thrombocytopenia on day 18 that was considered by the investigator to be related to AMG 780; this was a grade 3, non-serious adverse event and resulted in discontinuation of AMG 780.

- One subject in the 10-mg/kg dose group had a DLT of proteinuria on day 15 that was considered by the investigator to be related to AMG 780; this was a grade 3, non-serious adverse event and resulted in discontinuation of AMG 780. This DLT of grade 3, treatment-related proteinuria developed on day 15 from a worsening event of grade 2, non-related proteinuria that had been ongoing since day 2.
- One subject in the 30-mg/kg dose group had a DLT of pericardial effusion on day 4 that was considered by the investigator to be related to AMG 780 (a worsening of pericardial effusion that was present at baseline); this was a grade 3, serious adverse event. AMG 780 was discontinued due to disease progression.

Three fatal adverse events (1 event of suicide and 2 events of disease progression) were reported during the study; none of these were considered by the investigator to be related to AMG 780.

Adverse events of interest were observed for 32 (72.7%) subjects. The most frequent (occurring in > 10% of subjects) adverse events of interest were peripheral edema (29.5%), lymphopenia (20.5%), hypokalemia (13.6%), pleural effusion (13.6%), proteinuria (13.6%), and ascites (11.4%).

Of the 44 subjects included in the safety analysis set, 33 (75.0%) had at least 1 grade ≥ 2 laboratory abnormality after receiving AMG 780.

There were no grade 3 or 4 shifts in hemoglobin; 9 (20.5%) subjects had a grade ≥ 1 decrease and 4 (9.1%) subjects had a grade 2 decrease. Anemia was reported as an adverse event in 6 (13.6%) subjects (1 subject each in the 0.1-, 2.5-, 5-, and 10-mg/kg dose groups and 2 subjects in the 30 mg/kg dose groups).

One (2.3%) subject in the 0.6 mg/kg dose group had a grade 3 platelet decrease; this was reported as an adverse event of thrombocytopenia and was considered to be a DLT.

Lymphocyte decreases were $\geq$ grade 1 in 16 (36.4%) subjects, $\geq$ grade 2 in 13 (29.5%) subjects, and $\geq$ grade 3 in 7 (15.9%) subjects. Lymphopenia was reported as an adverse event in 9 (20.5%) subjects (1 subject each in the 0.3-, 0.6-, 1.2-, 2.5-, and 30-mg/kg dose groups and 2 subjects each in the 0.1- and 20-mg/kg dose groups).

No subjects were identified who met Hy's Law criteria for drug-induced liver injury.

Baseline and postbaseline serum amylase and lipase levels were within the normal limits across all treatment cohorts. There was no significant change in the baseline and postbaseline cortisol concentrations.

There was no significant difference in the baseline and postbaseline estimated glomerulation filtration rate values across the 9 treatment cohorts.

No important group trends were seen over time for vital signs.

No subject had a common terminology criteria for adverse events (CTCAE) grade 2 or grade 3 corrected QT interval using the Fridericia method (QTcF) prolongation. Change in QTcF values with increasing AMG 780 serum concentration did not suggest a trend towards dose-dependent QTcF prolongation.

Conclusions:

- AMG 780 demonstrated a tolerable safety profile in this FIH study.
- An MTD for AMG 780 was not determined; the highest dose tested was 30 mg/kg IV Q2W.
- After a single IV infusion, AMG 780 exhibited linear PK; C_{max} and AUC_{tau} increased dose proportionally. Steady state was reached after 3 Q2W doses and mean accumulation ratio was 1.6. The $t_{1/2,z}$ for the therapeutic dosing range ($\geq$ 2.5 mg/kg) varied between 8 and 13 days. For dose range 0.6 to 30 mg/kg, the mean estimated CL and V_{ss} were 0.16 mL/hr/kg and 31.4 mL/kg, respectively.

- No partial or complete responses were observed. Of the 35 evaluable subjects, 8 had stable disease as the best overall response; 1 subject had stable disease lasting > 6 months.
- The K^{trans} for 7 tumors in 6 subjects and IAUC for 6 tumors in 6 subjects decreased by > 20% at week 5 postdose relative to baseline. There was no apparent dose response trend for K^{trans} or IAUC.
- One subject tested positive for pre-existing, neutralizing binding AMG 780 antibodies at baseline but post treatment specimens were negative. The presence of neutralizing, anti-AMG 780 antibodies in this subject had no effect on serum AMG 780 concentrations.
- A dose-dependent increase from baseline in PLGF and sVCAM1 was revealed after AMG 780 administration; sKDR levels decreased over time. Neither baseline levels nor changes in CAFs were correlated to tumor response in these subjects.