2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: AMG 386

Name of Active Ingredient: AMG 386

Title of Study: A Randomized, Double-blind, Multi-center, Phase 2 Study to Estimate the Efficacy and Evaluate the Safety and Tolerability of Cisplatin & Capecitabine (CX) in Combination with AMG 386 or Placebo in Subjects with Metastatic Gastric, Gastroesophageal Junction, or Distal Esophageal Adenocarcinoma

Investigator(s) and Study Center(s): This study was conducted at 44 sites in Australia, Austria, Belgium, France, Hungary, the Netherlands, Poland, Spain, the United Kingdom, and the United States. Names and addresses of principal investigators are listed in Appendix 4.

Publication(s): None as of the date of this report

Study Period: 14 December 2007 (date first subject enrolled) to 15 December 2009 (primary analysis data cutoff date)

Development Phase: 2

Introduction and Objectives: A high proportion of resected gastric cancer specimens express angiopoietin-1 and -2 (Ang1 and Ang2), and over expression of Ang1 and Ang2 appears to be correlated with larger tumors and higher microvessel density (Moon, 2006). AMG 386 is a first-in-class antiangiogenic therapy that provides potent and selective inhibition of angiopoietins. AMG 386 inhibits angiogenesis by sequestering angiopoietin-1 and -2 (Ang1 and Ang2), thereby preventing their interaction with the Tie2 receptor. This study was designed to evaluate the activity of AMG 386 in subjects with metastatic gastric, gastroesophageal junction, or distal esophageal adenocarcinoma.

The primary objective of this phase 2, randomized, double-blind, placebo-controlled study was to estimate the treatment effect as measured by progression-free survival (PFS) of subjects receiving AMG 386 (at 2 doses) in combination with CX relative to CX/placebo.

The secondary objectives were to evaluate the safety and tolerability of the combination regimen of AMG 386 with CX; to estimate other measures of treatment effect (objective response rate, duration of response, overall survival, time to progression, and time to response); to evaluate the pharmacokinetics of AMG 386 when used in combination with CX; to estimate the immunogenicity as assessed by the incidence of anti-AMG 386 antibody formation; and to estimate the impact of AMG 386 on cancer-related symptoms based on patient-reported outcomes (PRO) using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Stomach 22 (QLQ-STO22).

[redacted]

[redacted]

Methodology: This phase 2, randomized, placebo-controlled, multi-center study was designed to estimate the treatment effect on PFS and response rate, and to evaluate the safety and tolerability of, AMG 386 in combination with CX compared to CX/placebo in the treatment of subjects with metastatic gastric cancer. Approximately 165 subjects were to be randomized 1:1:1 to each of the following arms:

- Arm A: Cisplatin 80 mg/m^2 intravenously (IV) once every 3 weeks (Q3W) + capecitabine 1000 mg/m^2 orally (PO) twice daily (BID) x 14 days Q3W + AMG 386 10 mg/kg IV once weekly (QW)
- Arm B: Cisplatin 80 mg/m^2 IV Q3W + capecitabine 1000 mg/m^2 PO BID x 14 days Q3W + AMG 386 3 mg/kg IV QW
- *Arm C: Cisplatin 80 mg/m^2 IV Q3W + capecitabine1000 mg/m^2 PO BID x 14 days Q3W + AMG 386 placebo IV QW*

Randomization was to be stratified by disease classification at enrollment (measurable vs nonmeasurable disease) and Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0 vs 1). Upon randomization each subject was to receive the first dose of CX and AMG 386 or placebo within 7 days. Subjects were to receive study treatment until radiographic disease progression per Response Evaluation Criteria in Solid Tumor (RECIST v 1.0) with modifications (Appendix 1), clinical progression, unacceptable toxicity, subject withdrawal of consent, or death. Subjects who discontinued for reasons other than withdrawal of full consent or death were requested to have a clinic visit or contact.

Radiological imaging to assess disease status was to be performed every 6 weeks ± 7 days (2 cycles) during the study until subjects developed radiographic disease progression. Any subject who discontinued study drug treatment prior to radiographic disease progression was to continue to have radiological imaging assessment performed every 6 weeks during the long-term follow-up period, provided they did not withdraw consent, until the subject developed radiographic disease progression or began a new treatment.

Subjects alive at the time of discontinuation of all study medications who did not withdraw full consent were to be contacted by telephone approximately every 3 months for up to 48 months from the date of the last subject's randomization to the trial, to assess overall survival and/or the commencement of additional cancer therapy.

Number of Subjects Planned: Approximately 165 subjects

Number of Subjects Enrolled: 171

Sex: 41 women (24%) and 130 men (76%)

Age: mean (standard deviation [SD]) 58.7 (10.4) years (range: 18 to 84 years)

Ethnicity (Race): 161 (94%) white or Caucasian, 1 (1%) black or African American, 4 (2%) Hispanic or Latino, 3 (2%) Asian, 1 (1%) Japanese, 1 (1%) other ethnicity

Diagnosis and Main Criteria for Eligibility: Eligible subjects were adults with histologically or cytologically confirmed adenocarcinoma of the stomach, gastroesophageal junction or distal esophagus with metastatic disease. Subjects could have measurable or nonmeasurable disease per RECIST v 1.0 with modifications, and ECOG performance status of 0 or 1. Subjects were required to have adequate organ and hematological function. Subjects were ineligible if they had received any prior chemotherapy for metastatic disease; if less than 12 months had elapsed from completion of previous adjuvant or neoadjuvant chemotherapy or chemoradiotherapy; if they had persistent gastric outlet obstruction, complete dysphagia or feeding jejunostomy; or if they had

received radiotherapy ≤ 14 days prior to randomization or had not recovered from radiotherapy-related toxicities.

Among other criteria, subjects could be excluded based on medical history of the following conditions: central nervous system metastases (current or prior); arterial or deep venous thromboembolism (within 12 months prior to randomization); clinically significant bleeding (within 6 months prior to randomization); major surgical procedure (within 28 days prior to randomization); minor surgical procedure (within 3 days prior to randomization); prior malignancy (with limited exceptions); or clinically significant cardiovascular diseases (within 12 months prior to randomization). Full inclusion and exclusion criteria are provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 386 and placebo were the only investigational products for this study. "Study drug" was defined as cisplatin, capecitabine and AMG 386 or placebo.

AMG 386 was to be administered IV QW at a dose of 3 mg/kg or 10 mg/kg. To maintain the double-blind in arms A, B, and C, each subject was to be infused weekly with a volume of investigational product equivalent to 10 mg/kg AMG 386. The manufacturing batch numbers of AMG 386 administered in this study were [redacted].

Placebo was to be administered IV QW and was to be presented in vials identical with those containing AMG 386. The weekly dose was to be a volume equivalent to 10 mg/kg AMG 386. The manufacturing batch numbers of placebo administered in this study were [redacted]

Duration of Treatment: Subjects were to receive study treatment until radiographic disease progression, clinical progression, unacceptable toxicity, subject withdrawal of consent, or death. The expected median duration of treatment was estimated as 6 months for subjects in Arm C and 8 months for subjects in Arms A and B.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: All subjects were to receive cisplatin 80 mg/m^2 as a 2-hour IV infusion on week 1 of every 3-week cycle, and capecitabine 1000 mg/m^2 orally, twice daily, for the first 14 consecutive days of each 3-week cycle. Cisplatin and capecitabine were obtained from commercial sources.

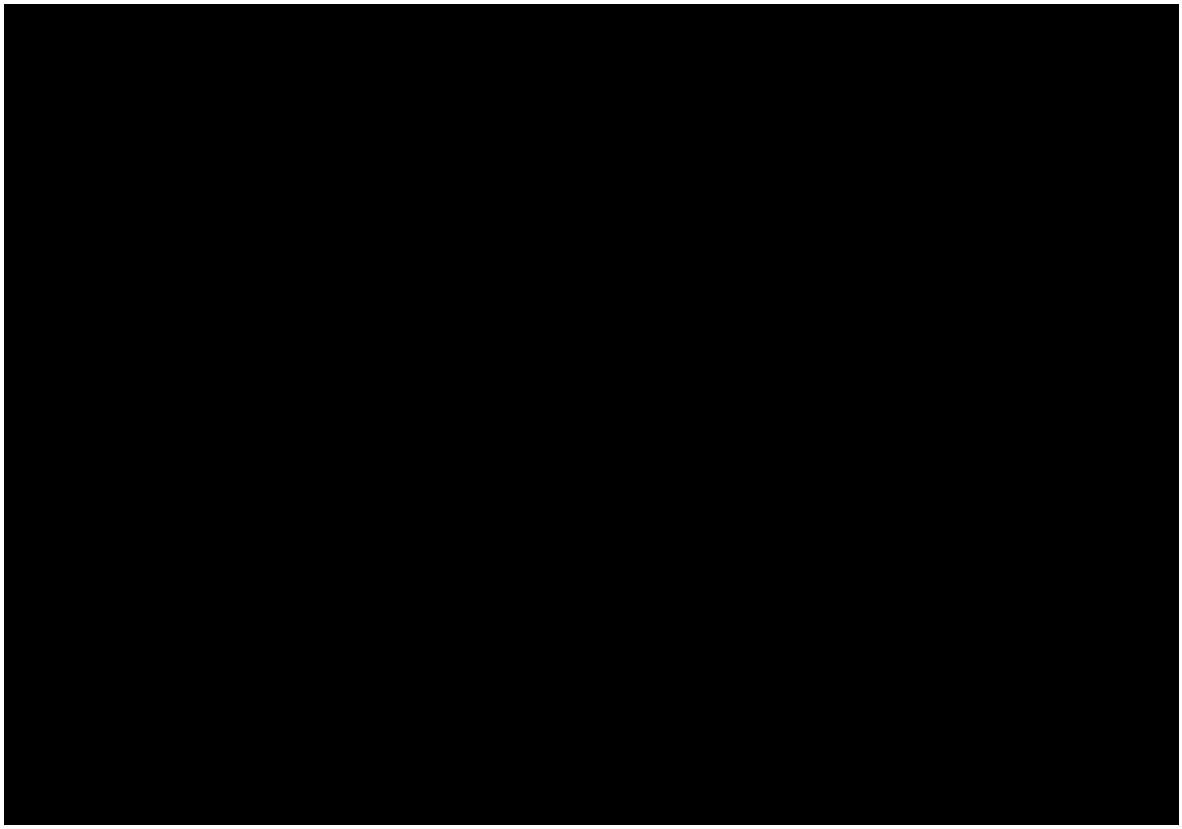
Study Endpoints

The primary endpoint was PFS, defined as time from date of randomization to date of disease progression (per RECIST v 1.0 with modifications) or death.

The secondary endpoints included the following:

- incidence of adverse events and significant laboratory changes from baseline
- objective response rate (ORR): the incidence of either confirmed complete response (CR) or confirmed partial response (PR) per RECIST v 1.0 with modifications
- duration of response (DOR): time from first confirmed objective response to disease progression (per RECIST v 1.0 with modifications) - (only calculated for those subjects who respond)
- overall survival (OS): time from date of randomization to date of death
- time to progression (TTP): time from date of randomization to date of disease progression per RECIST v 1.0 with modifications

- time to response: time from randomization date to date of first response for confirmed responders. Subjects with a best response of stable disease (SD) by the database cutoff date for analysis are censored at their last evaluable disease assessment date. Non-responders with a best response of progressive disease (PD) will be censored at the maximum time to a first confirmed response among all responders
- overall exposure, dose adjustments, and rates of discontinuation for cisplatin, capecitabine, and AMG 386
- pharmacokinetic parameters (maximum and minimum observed serum concentration [C_{max}, C_{min}]) of AMG 386 when used in combination with CX
- incidence of anti-AMG 386 antibody formation
- change in cancer-related symptoms as assessed with the QLQ-STO22



Statistical Methods: The goal of the primary statistical analysis was to estimate the treatment effect on PFS of AMG 386 in combination with CX compared to CX in combination with placebo in subjects with advanced gastric cancer. The primary analysis of the study was to occur when 113 PFS events had occurred, and was to be based upon investigator assessments of disease progression.

The primary analysis of PFS was to be conducted in the intent-to-treat (ITT) analysis set. Cox regression models stratified by the randomization factors (measurable vs nonmeasurable disease; ECOG status of 0 vs 1) were to be used to calculate hazard ratios and 2-sided 80% confidence intervals (CIs) for Arm A (CX + AMG 386 10 mg/kg) and Arm B (CX + AMG 386 3 mg/kg) combined relative to Arm C (CX + placebo). Hazard ratios and 2-sided 80% CIs were also to be calculated for the AMG 386 10-mg/kg arm relative to the 3-mg/kg arm, and for each AMG 386 arm (separately) relative to the placebo arm. Kaplan-Meier (K-M) curves and K-M medians, if estimable, were to be provided. A global ordered log-rank test stratified by the stratification factors was to be performed to assess any increasing trend in PFS among Arms C, B, and A. Stratified log-rank tests were to be used to perform pair wise comparisons of PFS

between Arms C and B and Arms B and A. Analyses of OS were to be performed as for PFS. Sensitivity analyses of PFS and TTP, and analyses of ORR, DOR, and time to response were to be conducted in the subset of subjects with measurable disease at baseline.

Safety assessments, including analyses of treatment-emergent adverse events; changes in laboratory values, electrocardiogram parameters, and vital signs; and the incidence of anti-AMG 386 antibody formation, were to be provided for all randomized subjects who received at least 1 dose of study drug.

PRO analyses were to be performed for subjects in the ITT analysis set with at least 1 PRO assessment prior to disease progression. Subject completion rates, dropout patterns, and PRO scores at each time point, including change from baseline, were to be summarized. [redacted]

Summary of Results:

Subject Disposition: Of 217 subjects screened, 171 subjects total were randomized 1:1:1 to receive CX plus AMG 386 10 mg/kg (Arm A), CX plus AMG 386 3 mg/kg (Arm B), or CX plus placebo (Arm C). Fifty-six of 56 subjects (100%), 58 of 59 subjects (98%), and 53 of 56 subjects (95%) randomized to the 3 arms, respectively, received at least 1 dose of study drug. At the time of the data cutoff for the primary analysis, most subjects (88%, 86%, and 84% in the CX/AMG 386 10-mg/kg, 3-mg/kg, and placebo arms, respectively) had ended all protocol-specified treatments. Eighty-eight percent, 86%, and 84% of subjects, respectively, had ended treatment with investigational product; 100%, 93%, and 91% had ended treatment with cisplatin; and 93%, 92%, and 86% had ended treatment with capecitabine.

Disease progression was the most common reason for discontinuation of investigational product (39%, 46%, and 57% of subjects in the CX/AMG 386 10-mg/kg, CX/AMG 386 3-mg/kg, and CX/placebo groups, respectively), and was also a common reason for discontinuation of cisplatin (29%, 31%, and 36% of subjects, respectively) and capecitabine (32%, 41%, and 50% of subjects, respectively). The proportion of subjects discontinuing investigational product due to adverse events was higher in the CX/AMG 386 10-mg/kg group than in the CX/AMG 386 3-mg/kg and CX/placebo groups (34%, 20%, and 7%, of subjects, respectively); the same was true for discontinuation of cisplatin (48%, 36%, 36%) and capecitabine (41%, 22%, 14%).

At baseline, the median sum of the longest diameters of target lesions was 89 mm, 88 mm, and 65 mm in the CX/AMG 386 10-mg/kg, 3-mg/kg, and CX/placebo groups, respectively, and the proportion of subjects with ≥ 3 sites of metastases was 29%, 36%, and 20%, respectively. No adjustment for these imbalances was made in the analyses of efficacy.

Efficacy Results: In the ITT population, the estimated hazard ratio (80% CI) for PFS in the AMG 386 arms (combined) relative to the placebo arm was 0.98 (0.77, 1.26), p = 0.92. Median PFS times in the CX/AMG 386 10-mg/kg, 3-mg/kg, and placebo arms were 4.2, 4.9, and 5.2 months, respectively. PFS hazard ratios (80% CIs) for pairwise comparisons of the treatment groups were 0.99 (0.74, 1.33), p = 0.96 (10-mg/kg arm vs placebo arm); 0.98 (0.74, 1.30), p = 0.93 (3-mg/kg arm vs placebo arm), and 1.04 (0.78, 1.40), p = 0.86 (10-mg/kg arm vs 3-mg/kg arm).

ORR (80% CI) was 27% (19, 37), 43% (34, 53), and 35% (27, 47), in the CX/AMG 386 10-mg/kg, 3-mg/kg, and placebo groups, respectively. Median (80% CI) TTP was 5.4 (4.1, 6.2), 5.4 (4.4, 5.8), and 5.3 (4.0, 6.6) months, respectively. The median (Q1, Q3) time to response (among

subjects who responded [n = 13, 22, and 17, respectively]) was 5.7 (5.3, 12.0) weeks, 5.9 (5.4, 11.4) weeks, and 6.0 (5.1, 11.1) weeks, respectively. Median (80% CI) DOR in responders was 7.8 (7.1, 16.6), 4.2 (4.1, 7.0), and 5.4 (4.1, 5.5) months, respectively. Time to response and DOR results must be interpreted with caution due to the small number of responders in each group.

As of the data cutoff date, 46%, 51%, and 61% of subjects in the CX/AMG 386 10-mg/kg, CX/AMG 386 3-mg/kg, and CX/placebo groups, respectively, were censored for OS. The estimated hazard ratio (80% CI) for OS in the AMG 386 arms (combined) relative to the placebo arm was 1.42 [1.03, 1.96], p = 0.16. Median OS was 9.1, 9.4, and 12.8 months in the CX/AMG 386 10-mg/kg, 3-mg/kg, and placebo groups, respectively. OS hazard ratios (80% CIs) for pairwise comparisons of the treatment groups were 1.51 (1.05, 2.17), p = 0.15 (10-mg/kg arm vs placebo arm), 1.32 (0.91, 1.92), p = 0.34 (3-mg/kg arm vs placebo arm), and 1.16 (0.83, 1.63), p = 0.57 (10-mg/kg arm vs 3-mg/kg arm). A lower proportion of subjects in the CX/AMG 386 10-mg/kg group, relative to the 3-mg/kg and placebo groups, received subsequent systemic anti-cancer therapy after discontinuation of investigational product (21%, 35%, and 36%, respectively, of those who discontinued for reasons other than death, withdrawal of full consent, or lost to follow-up).

Pharmacokinetics Results: The median AMG 386 C_{max} and C_{min} values at steady state following co-administration with capecitabine and cisplatin were dose proportional, and co-administration with capecitabine and cisplatin was not observed to markedly affect AMG 386 exposure in this study. Median platinum (total and unbound) C_{max} values on week 1 and week 10 appeared to be similar in placebo and AMG 386-treated subjects. [redacted] Based on the population pharmacokinetics analysis, baseline creatinine clearance was found to be a significant covariate for AMG 386 clearance. No association between AUC_{ss} and PFS was observed.

Antibody Results: Non-neutralizing, anti-AMG 386 binding antibodies were transiently detected in 2 of 73 subjects (2.7%) in the CX/AMG 386 arms (combined). Preexisting, non-neutralizing antibodies were observed in 2 of 49 subjects (4.1%) in the CX/placebo arm. No subject tested positive for neutralizing antibodies during the study.

Patient-reported Outcomes Results: In an analysis using a linear mixed model, significant treatment differences favoring AMG 386 were seen in the overall LS adjusted means for QLQ-STO22 dysphagia scale (-7.08; 95% CI, -12.66, -1.50) and the QLQ-C30 diarrhea scale (-7.77; 95% CI, -15.50, -0.05). Numerical differences between treatment groups favoring AMG 386 were observed in a majority of the estimates for the other scales (ie, pain, reflux, eating restrictions, dry mouth, taste, emotional functioning, nausea and vomiting, pain, appetite loss, and quality of life). Sensitivity analysis using pattern mixture models were generally consistent with the linear model results suggesting that missing data due to dropouts has little impact on the PRO scores.

Biomarker Results: [redacted]

Safety Results: Subjects in the CX/AMG 386 10-mg/kg group received fewer infusions of investigational product than those in the CX/AMG 386 3-mg/kg or CX/placebo groups (median [Q1, Q3]: 12 [7, 25], 18 [8, 27] and 17 [6, 27] infusions, respectively). The median (Q1, Q3) cumulative dose of capecitabine was 83552 (51301, 136935) mg/m^2, 115198 (56735, 173120) mg/m^2, and 120709 (54000, 224142) mg/m^2 in the CX/AMG 386 10-mg/kg, 3-mg/kg, and CX/placebo groups, respectively; reduced exposure in the AMG 386 arms appeared to be due primarily to earlier treatment discontinuation (predominantly, earlier treatment discontinuation due to adverse events). The median (Q1, Q3) cumulative dose of cisplatin was 310 (162, 450)

mg/m^2, 338 (162, 476) mg/m^2, and 320 (160, 487) mg/m^2 in the CX/AMG 386 10-mg/kg, 3-mg/kg, and CX/placebo groups, respectively.

The overall subject incidence of adverse events was similar across the CX/AMG 386 10-mg/kg, CX/AMG 386 3-mg/kg, and CX/placebo groups (96%, 100%, and 100%, respectively). No consistent trend was observed in the subject incidence of grade 3 or grade 4 adverse events, but the subject incidence of grade 5 (fatal) events was higher in the AMG 386 arms relative to placebo (13%, 16%, 8%, respectively), as was the subject incidence of serious adverse events (73%, 60%, 47%) and adverse events leading to withdrawal from the treatment phase or from the study (30%, 26%, 9%, respectively).

Common adverse events leading to discontinuation of investigational product included pulmonary embolism (5%, 2%, 4%), diarrhea (2%, 5%, 0%), and nausea (4%, 3%, 0%). Common adverse events leading to discontinuation of cisplatin included nausea (7%, 3%, 2%), decreased creatinine renal clearance (0%, 7%, 4%), vomiting (2%, 5%, 2%), pulmonary embolism (5%, 2%, 0%) and peripheral sensory neuropathy (4%, 3%, 4%). Common adverse events leading to discontinuation of capecitabine included nausea (7%, 2%, 0%), vomiting (5%, 3%, 2%), diarrhea (2%, 5%, 0%), fatigue (0%, 5%, 0%), and pulmonary embolism (4%, 2%, 0%). Of note, while pulmonary embolism was among the most common reasons for discontinuation of all 3 study drugs, the overall subject incidence of pulmonary embolism (including events not leading to discontinuation) was lower in the CX/AMG 386 groups than in the CX/placebo group (9%, 3%, and 15%, respectively).

A higher subject incidence in either the CX/AMG 386 10-mg/kg or 3-mg/kg group relative to the CX/placebo group (based on a cutoff of 10% absolute difference) was observed for the following MedDRA preferred terms: fatigue (39%, 53%, 36%, respectively), decreased appetite (30%, 53%, 43%), diarrhea (45%, 52%, 42%), constipation (48%, 43%, 34%), abdominal pain (30%, 40%, 17%), peripheral edema (13%, 29%, 6%), hypertension (5%, 14%, 4%; no grade 3 or higher events), and deep vein thrombosis (11%, 12%, 2%).

Treatment-related adverse events occurred in 95%, 95%, and 89% of subjects in the CX/AMG 386 10-mg/kg, CX/AMG 386 3-mg/kg, and CX/placebo groups (Table 11-1). Adverse events were reported as related to treatment with AMG 386 (or placebo) for 54%, 72%, and 66% of subjects, respectively; to cisplatin for 93%, 91%, and 87% of subjects, respectively; and to capecitabine for 91%, 95%, and 85% of subjects, respectively.

Edema, an identified risk of AMG 386 administration, was reported in 25%, 40%, and 15% of subjects in the CX/AMG 386 10-mg/kg, 3-mg/kg, and CX/placebo groups, respectively, with 1 event of grade 3 or higher (3 mg/kg arm). Hypertension, an adverse event of interest, was reported as an adverse event in 5%, 14%, 4% of subjects, respectively, with no grade 3 or higher events. The subject incidence of other adverse events of interest and potential risks (arterial and venous thromboembolic events, cardiac toxicity, gastrointestinal perforation, hemorrhage, hematologic toxicity, hypertension, hypothyroidism, impaired wound healing, pancreatic toxicity, proteinuria, and infusion reaction) was similar (within 5 percentage points) or lower in each of the CX/AMG 386 arms relative to the CX/placebo arm.

Laboratory test results were generally similar between the CX/AMG 386 and CX/placebo arms. The subject incidence of grade 3 and higher abnormal laboratory values was similar in the CX/AMG 386 and CX/placebo arms. No neutralizing antibodies were observed.

Conclusions: The hazard ratio point estimate indicates similar PFS between the CX/AMG 386 and CX placebo arms; based on the 80% CI, this result is consistent with any drug effect between a 23% improvement and a 26% worsening in PFS. While the study was not powered to test differences in OS (a secondary endpoint), the hazard ratio point estimate for OS indicates longer OS in the placebo arm; based on the 80% CI, this result is consistent with a 3% to 96%

worsening in OS in the AMG 386 arms. Survival data are not fully mature at the time of this analysis and will be further described in a future report.

The rate of treatment discontinuation due to adverse events was higher in the AMG 386 arms relative to placebo. Other than marginal increases in the expected toxicities of the CX regimen (diarrhea, nausea, vomiting), no single specific toxicity appeared to account for the discontinuation of therapy in the AMG 386 arms, and no unexpected toxicities were apparent. It is possible that the addition of AMG 386 reduced the tolerability of the CX regimen. Imbalance in baseline characteristics may have also contributed to reduced tolerability to study treatment in the AMG 386 arms.

Early discontinuation of the study treatment and lower cumulative exposure to capecitabine in the AMG 386 arms, however, did not result in inferior PFS or TTP. More subjects in the AMG 386 arms experienced deaths due to disease progression than in the placebo arm. Multiple factors, notably the imbalance in baseline characteristics related to tumor burden, and post-progression anti-cancer therapy, may have contributed to the observed difference in the number of deaths due to disease progression in this study.

Among those subjects with an objective response, DOR was increased at the highest dose of AMG 386. Further biomarker analysis may be warranted.

Co-administration with capecitabine and cisplatin was not observed to markedly affect AMG 386 exposure in this study. No association between AUC_{ss} and PFS was observed.

2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Trebananib (also known as AMG 386; hereinafter referred to as trebananib)

Name of Active Ingredient: Trebananib

Title of Study: A Randomized, Double Blind, Multi-Center, Phase 2 Study to Estimate the Efficacy and Evaluate the Safety and Tolerability of Cisplatin & Capecitabine (CX) in Combination with AMG 386 or Placebo in Subjects with Metastatic Gastric, Gastroesophageal Junction, or Distal Esophageal Adenocarcinoma

Investigators and Study Centers: This study enrolled subjects at 40 sites in Australia, Austria, Belgium, France, Hungary, the Netherlands, Poland, Spain, the United Kingdom, and the United States. Names and addresses of principal investigators are listed in Appendix 2.

Publications: Eatock M, Tebbutt N, Bampton C, et al. Phase 2 randomized, double-blind, placebo-controlled study of AMG 386 in combination with cisplastin and capecitabine in patients with metastatic gastro-oesophageal cancer. *Annals of Oncology*. 2012; In press.

Eatock M, Szanto J, Tebbutt N, et al. Randomized, double-blind, placebo-controlled phase 2 study of AMG 386 in combination with cisplatin and capacitabine (CX) in patients (Pts) with metastatic gastro-esophageal adenocarcinoma [poster]. Gastrointestinal Cancers Symposium; 20–22 January 2011; San Francisco, CA.

Study Period: 14 December 2007 (date first subject enrolled) to 25 May 2012 (study early discontinuation date)

Development Phase: 2

Introduction and Objectives: This study was designed to evaluate the activity of trebananib, an antiangiogenic investigational product, in subjects with metastatic gastric, gastroesophageal junction, or distal esophageal adenocarcinoma. Results of the primary analysis in December 2009 were described in a full study report. At the time of the primary analysis report data cut-off, there were 7 (13%), 7 (12%), and 6 (11%) subjects in the 10 and 3 mg/kg trebananib and placebo dose groups who were continuing in the study with at least one study drug. This abbreviated report summarizes data from the final analysis.

The primary objective of this phase 2, randomized, double-blind, placebo-controlled study was to estimate the treatment effect as measured by progression-free survival (PFS) of subjects receiving trebananib (at 2 doses) in combination with CX relative to CX/placebo. The secondary objectives were to evaluate the safety and tolerability of the combination regimen of trebananib with CX; to estimate other measures of treatment effect (objective response rate [ORR], duration of response [DOR], overall survival [OS], time to progression [TTP], and time to response [TTR]); to evaluate the pharmacokinetics (PK) of trebananib when used in combination with CX; to estimate the immunogenicity as assessed by the incidence of anti-trebananib antibody formation; and to estimate the impact of trebananib on cancer-related symptoms based on patient-reported outcomes (PRO) using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Stomach 22 (QLQ-STO22). Exploratory objectives are described in the study protocol (Appendix 1).

Methodology: Subjects were randomized 1:1:1 to the following treatment arms:

- Arm A: Cisplatin 80 mg/m^2 intravenously (IV) once every 3 weeks (Q3W) + capecitabine 1000 mg/m^2 orally (PO) twice daily (BID) x 14 days Q3W + trebananib 10 mg/kg IV once weekly (QW)
- Arm B: Cisplatin 80 mg/m^2 IV Q3W + capecitabine 1000 mg/m^2 PO BID x 14 days Q3W + trebananib 3 mg/kg IV QW

- Arm C: Cisplatin 80 mg/m^2 IV Q3W + capecitabine1000 mg/m^2 PO BID x 14 days Q3W + trebananib placebo IV QW

Radiological imaging to assess disease status was to be performed every 6 weeks ± 7 days (2 cycles) during the study until subjects developed radiographic disease progression, withdrew consent, or started a new treatment. Subjects received study treatment until radiographic disease progression per Response Evaluation Criteria in Solid Tumor (RECIST v 1.0) with modifications (Appendix 1), clinical progression, unacceptable toxicity, withdrawal of consent, or death. Subjects were to return for a safety follow-up visit between 30 and 37 days from discontinuation of study treatment, and were followed for survival for up to 48 months from the date the last subject was randomized. Subjects who withdrew consent were not permitted to participate in the long-term follow-up period.

Number of Subjects Planned: Approximately 165 subjects

Number of Subjects Enrolled: 171

Sex: 41 women (24%) and 130 men (76%)

Age: mean (standard deviation [SD]) 58.7 (10.4) years (range: 18 to 84 years)

Ethnicity (Race): 161 (94%) white or Caucasian, 1 (1%) black or African American, 4 (2%) Hispanic or Latino, 3 (2%) Asian, 1 (1%) Japanese, 1 (1%) other ethnicity

Diagnosis and Main Criteria for Eligibility: Eligible subjects were adults with histologically or cytologically confirmed adenocarcinoma of the stomach, gastroesophageal junction, or distal esophagus with metastatic disease. Subjects could have measurable or nonmeasurable disease per RECIST v 1.0 with modifications. Subjects were ineligible if they had received any prior chemotherapy for metastatic disease; if less than 12 months had elapsed from completion of previous adjuvant or neoadjuvant chemotherapy or chemoradiotherapy; if they had persistent gastric outlet obstruction, complete dysphagia or feeding jejunostomy; or if they had received radiotherapy ≤ 14 days prior to randomization or had not recovered from radiotherapy-related toxicities.

Investigational Product, Dose and Mode of Administration, Manufacturing Lot Number: Trebananib was administered IV QW at a dose of 3 mg/kg or 10 mg/kg. To maintain the double-blind in arms A, B, and C, each subject was to be infused weekly with a volume of study drug equivalent to 10 mg/kg trebananib. Placebo was administered IV QW and was presented in vials identical with those containing trebananib. The manufacturing batch numbers of trebananib administered in this study were [redacted]. The manufacturing batch numbers of placebo administered in this study were [redacted].

Duration of Treatment: Subjects were to receive study treatment until radiographic disease progression, clinical progression, unacceptable toxicity, subject withdrawal of consent, or death.

Reference Therapy, Dose and Mode of Administration, Manufacturing Lot Number: All subjects were to receive cisplatin 80 mg/m^2 as a 2-hour IV infusion on week 1 of every 3-week cycle, and capecitabine 1000 mg/m^2 PO BID for the first 14 consecutive days of each 3-week cycle. Cisplatin and capecitabine (CX) were obtained from commercial sources.

Study Endpoints: The primary endpoint was PFS, defined as the time from randomization date to date of disease progression (per RECIST v 1.0 with modifications) or death. Secondary efficacy endpoints included the incidence of adverse events and significant laboratory changes from baseline; ORR; DOR; OS; TTP, TTR; overall exposure, dose adjustments, and rates of discontinuation for cisplatin, capecitabine, and trebananib; PK parameters (maximum and minimum observed serum concentration [C_{max}, C_{min}]) of trebananib when used in combination with CX; incidence of anti-trebananib antibody formation; and change in cancer-related symptoms

as assessed with the QLQ-STO22. Exploratory endpoints are described in the study protocol (Appendix 1).

Statistical Methods: PFS and OS were evaluated in the All Randomized analysis set. Cox regression models stratified by the randomization factors were used to calculate PFS and OS hazard ratios and 2-sided 80% confidence intervals (CIs) for the trebananib arms combined relative to the placebo arm, and for pairwise comparisons among all 3 arms. Kaplan-Meier (K-M) curves and K-M medians were provided. A global ordered log-rank test stratified by the stratification factors was performed to assess any increasing trend in PFS among Arms C, B, and A. Stratified log-rank tests were used to compare PFS between Arms C and B and Arms B and A. Sensitivity analyses of PFS and TTP, and analyses of ORR, DOR, and TTR were conducted in the subset of subjects with MDB.

Trebananib, cisplatin, capecitabine, and 5-fluorouracil (5-FU) individual serum concentrations and summary statistics for each dose group were provided. PK data analyses were performed by the Department of Pharmacokinetics and Drug Metabolism at Amgen Inc. Descriptive statistics of the individual AMG 386 C_{min} and C_{max} values when administered with CX were summarized using WinNonlin Enterprise software (Version 5.1.1, [redacted]) as part of the validated PKS system. Details on the PK analysis methods are provided in the clinical study report for the primary analysis.

Safety assessments, including analyses of treatment-emergent adverse events; changes in laboratory values, electrocardiogram (ECG) parameters, and vital signs; and the incidence of anti-trebananib antibody formation, were provided for all randomized subjects who received at least 1 dose of study drug.

Summary of Results:

Subject Disposition:

Subject enrolled: 171 (56 to AMG 386 10 mg/kg + CX [Arm A]; 59 to AMG 386 3 mg/kg + CX [Arm B]; 56 to placebo + CX [Arm C])

Subjects who received study drug during the study: 167

Subjects included in efficacy analyses: 171

Subjects included in safety analyses: 167

Deaths (Safety Population): 136 (46 in Arm A; 47 in Arm B; 43 in Arm C); 23 subjects died within 37 days of last dose of study drug

The most frequently reported reasons overall across all treatment arms for ending trebananib/placebo, cisplatin, and capecitabine treatment were disease progression (56%, 32%, 46%, respectively) and adverse event (22%, 42%, 27%, respectively).

Efficacy Results:

Results for PFS, ORR, DOR, OS, TTP, TTR, and change in tumor burden were consistent with those of the Primary Analysis Report.

Median PFS times in the CX/trebananib 10 mg/kg, 3 mg/kg, and placebo arms were 4.4, 5.2, and 5.3 months, respectively, and the median PFS time for the both CX/trebananib arms combined was 4.9 months. In the full analysis of the primary analysis of PFS, a Cox regression model stratified by the randomization stratification factors provided a hazard ratio (80% CI) of 1.03 (0.82, 1.28), p = 0.88, for the 2 CX/trebananib arms (combined) relative to the CX/placebo arm. Similarly, in a secondary analysis in the full analysis, hazard ratios for pairwise comparisons of the treatment groups were all close to 1. In another secondary analysis, a global ordered log-rank test found no evidence of a dose response for PFS (p = 0.73).

Median (80% CI) OS was 9.1 (7.3, 10.8) months, 8.8 (7.2, 9.4) months, and 12.8 (9.4, 15.2) months in the CX/trebananib 10 mg/kg, CX/trebananib 3 mg/kg, and CX/placebo groups, respectively. A stratified Cox regression analysis of OS in the 2 CX/trebananib groups (combined) vs the CX/placebo group favored the CX/placebo group; however, it was not statistically significant (hazard ratio [80% CI]: 1.22 [0.96, 1.54], p = 0.30).

Similar to previous observations, anti-trebananib (binding and neutralizing) antibodies, when tested positive at baseline or postbaseline, do not alter trebananib pharmacokinetics. The biomarker results are reported in the Primary Analysis Report.

Safety Results:

The types of adverse events reported in subjects in the CX/trebananib 10 mg/kg and 3 mg/kg groups were generally consistent with those reported in the primary analysis. The incidence of treatment-emergent adverse events (any grade) was similar across the CX/trebananib 10 mg/kg, CX/trebananib 3 mg/kg, and CX/placebo groups (96%, 100%, and 100% of subjects, respectively). The adverse event preferred terms with the highest subject incidence (≥ 20%) in any trebananib arm in descending order included nausea, fatigue, decreased appetite, vomiting, diarrhea, constipation, neutropenia, abdominal pain, anemia, edema peripheral, palmar-plantar erythrodysaesthesia syndrome (PPE), upper abdominal pain, asthenia, the events of each which were primarily grade ≤ 3. A higher incidence in either the CX/trebananib 10 mg/kg or 3 mg/kg group relative to the CX/placebo group (based on a cutoff of a ≥ 10% absolute difference) was reported for fatigue (39%, 55%, 36%, respectively), decreased appetite (32%, 55%, 43%), diarrhea (46%, 52%, 42%), constipation (48%, 43%, 34%), abdominal pain (32%, 40%, 19%), peripheral edema (14%, 29%, 6%), hypertension (5%, 14%, 4%; no grade 3 or higher events), and deep vein thrombosis (11%, 12%, 2%). Subject incidence of grade 3 or higher adverse events was highest in the CX/trebananib 3 mg/kg treatment group (86%) vs the CX/trebananib 10 mg/kg treatment group and placebo group (80% and 75%, respectively). Grade 3 (or higher) adverse events that were more frequently reported in the 10 mg/kg or 3 mg/kg treatment arms relative to the placebo (by ≥ 5%) included deep vein thrombosis (12% and 11% vs 2%, respectively) and abdominal pain (3% and 18% vs 4%, respectively).

Treatment-related adverse events occurred in 95%, 95%, and 89% of subjects in the CX/trebananib 10 mg/kg, CX/trebananib 3 mg/kg, and CX/placebo groups, respectively.

Serious adverse events occurred more often in either the CX/trebananib 10 mg/kg or 3 mg/kg arms relative to the placebo (73% and 60% vs 49%, respectively). The most frequently reported serious adverse events (≥ 10% of subjects in any of the trebananib arms) were vomiting, nausea, anemia, abdominal pain, pulmonary embolism, and febrile neutropenia, and these preferred terms were also among the most frequently reported serious adverse events considered related to trebananib. Serious adverse events considered by the investigator to be related to any study treatment were also more frequently reported in subjects receiving trebananib, occurring in 46%, 45%, and 32% of subjects in the 3 groups, respectively.

There were a total of 136 deaths in subjects in the Safety Set (46 [82%], 47 [81%], and 43 [81%] subjects in the CX/trebananib 10 mg/kg, CX/trebananib 3 mg/kg, and CX/placebo groups, respectively). Deaths were most frequently attributed to disease progression (70%, 71%, and 74% of subjects, respectively). Deaths considered by the investigator as due to adverse events also occurred with similar frequency across the 3 treatment groups (7%, 5%, and 4% of subjects, respectively). The incidence of grade 5 adverse events was higher in the trebananib treatment arms (10 mg/kg and 3 mg/kg) relative to placebo (13% and 17% vs 8%, respectively).

Identified risks for trebananib include ascites, pleural effusion, edema, and blurred vision. The subject incidence of edema adverse events was higher in the CX/trebananib 10 mg/kg and 3 mg/kg arms compared to the CX/placebo arm (29% and 41% vs 17%, respectively). The most frequently reported edema adverse event was peripheral edema (14% and 29% vs 6%, respectively). Ascites was reported in 5%, 5%, and 2% of subjects, respectively; pleural effusion in 5%, 3%, and 0% of subjects, respectively; and blurred vision in 5%, 0%, and 0% of subjects, respectively.

Potential risks for trebananib administration include pulmonary embolism, proteinuria, gastrointestinal perforation, hemorrhagic events, and infusion reactions. Pulmonary embolism was reported in 9%, 3%, and 15% of subjects in the CX/trebananib 10 mg/kg and 3 mg/kg, and CX/placebo arms, respectively. Incidences of potential risks were similar across treatment groups for proteinuria, gastrointestinal perforation, and hemorrhagic events. Hemorrhagic events consisted of a variety of events including hematemesis, melena, rectal, gastric, contusion, hematuria, epistaxis, and hemoptysis, which occurred in similar frequencies across the

CX/trebananib 10 mg/kg and 3 mg/kg, and CX/placebo treatment arms. Infusion reactions were reported in 2% (dyspnea only), 3% (both dyspnea and pyrexia), and 2% (pyrexia only), of subjects, respectively. The infusion reactions were either grade 1 or 2, and none were serious or assessed as related by the investigator to trebananib administration.

Other adverse events of interest for trebananib included arterial and venous thromboembolic events, cardiac toxicity, hematologic toxicity, hypertension, hypothyroidism, impaired wound healing, hypokalemia, and pancreatic toxicity. With the exception of hypertension assessed as an adverse event, the subject incidence of each of these adverse events of interest was similar (within 5 percentage points) or lower in each of the CX/trebananib arms relative to the CX/placebo arm. Hypertension was more frequently reported as an adverse event in the CX/trebananib 3 mg/kg group (14%) as compared to the 10 mg/kg group (5%) or placebo (4%).

Although decreases of 1 or 2 toxicity grades from baseline in serum potassium were more common in subjects receiving trebananib than in those receiving placebo (27%, 37%, and 19% of subjects in the CX/trebananib 10 mg/kg, 3 mg/kg, and CX/placebo groups, respectively), the subject incidence of shifts of ≥ 3 grades was similar among the 3 arms. Hematological toxicity was assessed as incidence of adverse events and through changes in laboratory values and was specified adverse event of interest for this study. Shifts of ≥ 3 toxicity grades from baseline in platelet counts occurred in 4%, 2%, and 11% of subjects in the CX/trebananib 10 mg/kg, 3 mg/kg, and CX/placebo groups, respectively; shifts of ≥ 3 toxicity from baseline in hemoglobin levels occurred in 4%, 0%, and 0% of subjects, respectively; and shifts of ≥ 3 toxicity grades from baseline in total neutrophils occurred in 18%, 35%, and 29%, respectively. Urine protein and blood urea nitrogen shift from baseline grade results were similar across the 3 treatment arms.

For most individuals, systolic and diastolic blood pressures were relatively stable over the course of the study, and values in the 3 treatment arms appeared similar. The analysis of ECG indicated that the maximum post-baseline QT interval with Fridericia's correction (QTcF) value was an average of 420, 423, and 434 msec in the CX/trebananib 10 mg/kg, 3 mg/kg, and CX/placebo groups, respectively. The maximum increase in QTcF from baseline was a median of 19, 15, and 8 msec in the 3 groups, respectively. A categorical analysis identified 2 subjects subject [redacted]) in the primary analysis with QTcF > 500 msec and/or increased > 60 msec from baseline. Subject [redacted] had a history of pulmonary embolism (2005). At baseline, the QTc was normal, and after the first dose of IP the QTc was prolonged at week 1 to 517 msec. One month later the subject developed fatal pulmonary embolism, and fatal acute myocardial infarction. In subject [redacted], there was no baseline QTc value reported. The QTcF was 521 msec (post-infusion) at week one, and then returned to normal thereafter. This subject was not symptomatic, and there were no adverse events reported associated with this event.

Antibody Results: Developing non-neutralizing anti-trebananib antibodies were transiently detected in 2 of 78 subjects (2.6%) treated with trebananib.

Pharmacokinetic Results: An additional 69 PK samples were received and analyzed after the primary PK analysis was performed. The majority of the 69 new trebananib PK samples were collected at safety follow-up or during unscheduled visits. The trebananib concentrations for these samples were consistent with the range of trebananib concentrations observed at the time of the primary analysis. The outcome of any queries that were outstanding at the time of the primary analysis did not impact any of the previously reported results. PK analysis was performed at the time of the primary analysis clinical study report. The median trebananib C_{max} and C_{min} values at steady state following co-administration with CX in subjects with metastatic gastric, gastroesophageal junction, or distal esophageal adenocarcinoma were dose-proportional. Co-administration with CX was not observed to markedly affect trebananib exposure. Median platinum (total and unbound) C_{max} values on week 1 and week 10 appeared to be similar in placebo and trebananib-treated subjects. The effect of trebananib on the PK of capecitabine and 5-FU could not be evaluated due to data limitations (incomplete dosing records).

Conclusions: The results of the final analysis were consistent with those of the primary analysis in this randomized, placebo-controlled phase 2 estimation study. The primary endpoint of PFS was similar with trebananib (10 or 3 mg/kg QW) plus CX and placebo plus CX treatment among

subjects with metastatic gastro-oesophageal cancer. The types of adverse events reported in subjects in the CX/trebananib 10 mg/kg and 3 mg/kg groups were generally consistent with those reported in previous trebananib studies. Although clinically manageable, toxicity was greater with trebananib plus CX compared with placebo plus CX.