2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: ganitumab (AMG 479)

Name of Active Ingredient: ganitumab

Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of AMG 479 or Placebo in Combination with Gemcitabine as First-line Therapy for Metastatic Adenocarcinoma of the Pancreas

Investigators and Study Centers: This study was conducted at 170 centers in 32 countries. Centers and principal investigators are listed in Section 16.1.4.

Publication: None

Study Period: 07 April 2011 to 12 December 2012

Development Phase: 3

Objectives:

The primary objective was to determine if the treatment of ganitumab at 12 mg/kg and/or 20 mg/kg in combination with gemcitabine improves overall survival (OS) as compared with placebo in combination with gemcitabine in subjects with metastatic adenocarcinoma of the pancreas.

Secondary Objectives:

- to evaluate progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- to evaluate the survival rate at 12-months, and at the timepoints of 3, 6, 9, 18, and 24 months; to evaluate objective response rate, time to disease progression, duration of response, and disease control rate (partial response [PR] + complete response [CR] + stable disease [SD]) as per RECIST version 1.1
- to evaluate subject incidence of adverse events, significant laboratory abnormalities, and immunogenicity
- to evaluate ganitumab dose exposure, dose intensity, and pharmacokinetics (PK) parameters and to evaluate relationships between ganitumab exposure measures and selected safety and efficacy measures
- to evaluate gemcitabine dose exposure, dose intensity in all subjects, and gemcitabine PK parameters in a subset of subjects; to evaluate patient reported hepatobiliary symptoms measured by the Functional Assessment of Cancer Therapy Hepatobiliary subscale questionnaire (FACT-Hep-HS)
- to evaluate the efficacy of ganitumab vs placebo in combination with gemcitabine within an enriched sub-population defined by a single or composite biomarker [redacted] with respect to OS

Exploratory objectives are listed in protocol Section 1.3 (Section 16.1.1 of this report).

Methodology: This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study. The study was designed to evaluate ganitumab (intravenous [IV] infusion of 12 or 20 mg/kg) or placebo on days 1 and 15 of a 28-day cycle in combination with gemcitabine (IV infusion of 1000 mg/m^2) on days 1, 8, and 15 of a 28-day cycle. After screening assessments and meeting all eligibility criteria, subjects were randomized in a 2:2:1 ratio to receive placebo, ganitumab 12 mg/kg or 20 mg/kg in combination with gemcitabine. Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), the presence of liver metastases (yes vs no), and by geographical region (Western Europe, United States, Canada, Australia vs rest of world).

Gemcitabine 1000 mg/m^2 over 30 (± 10) minutes IV infusion was administered as an open-label treatment followed by placebo, ganitumab at 12 mg/kg or 20 mg/kg as double-blind treatment. Subjects received protocol-specific therapy until radiographic disease progression (per RECIST version 1.1), unacceptable toxicities, withdrawal of consent, or start of a new systemic anti-cancer therapy.

Subjects were evaluated using radiographic imaging for tumor response every 8 weeks (± 7 days) independent of the treatment cycle until disease progression, withdrawal of consent, or initiation of new systemic anti-cancer therapy. All subjects were assessed for non-intensive ganitumab PK. Approximately 13 evaluable subjects per arm were assessed for intensive PK of ganitumab and gemcitabine (and gemcitabine metabolite). All subjects were assessed for a safety follow-up 30 (+3) days after the last dose of last protocol specified therapy. Subjects who discontinued treatment were followed for safety, immunogenicity, and PK at the day 30 (+3) days safety follow up visit and for post-protocol therapy and survival every 12 weeks (± 14 days) from the date of last dose of last protocol-specified therapy during long-term follow-up.

An independent Data Monitoring Committee (DMC) external to Amgen was established to conduct 2 planned safety and 1 interim efficacy reviews. The 2 safety reviews occurred after 50 subjects (approximately 20, 20, and 10 per arm) and 150 subjects (approximately 60, 60, and 30 per arm) had been enrolled and had the opportunity to complete 1 cycle of protocol-specified therapy. Thereafter, the DMC safety reviews were to occur approximately every 6 months until the primary analysis had been completed. This occurred without a hold in enrollment. The interim analysis of OS for lack of benefit for ganitumab 12 mg/kg and/or ganitumab 20 mg/kg vs placebo was performed at approximately 30% (188 events) of the primary analysis total event goal.

This study was terminated early (12 December 2012), following the review of the pre-planned interim efficacy analysis by the DMC. There were no safety concerns raised in the DMC review of the study. However, the DMC concluded that the addition of ganitumab to gemcitabine is unlikely to demonstrate a statistically significant improvement in the primary endpoint of OS, compared to gemcitabine alone.

Number of Subjects Planned: Approximately 825 subjects

Diagnosis and Main Criteria for Eligibility: This study enrolled men and women ≥ 18 years of age, with histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas (American Joint Committee on Cancer Stage IV); ECOG score of 0 or 1. Subjects were excluded if they had an Islet cell, acinar cell carcinoma, non-adenocarcinoma, (eg, lymphoma, sarcoma, etc), adenocarcinoma originated from biliary tree, or cystadenocarcinoma; currently treated or previously treated with biologic, small molecule, immunotherapy, chemotherapy (eg, gemcitabine), radiotherapy, chemoradiotherapy, or other agents for pancreatic cancer. A full list of inclusion and exclusion criteria is provided in Protocol Section 4 (Section 16.1.1 of this report).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects were administered 12 or 20 mg/kg of ganitumab and ganitumab-placebo by IV infusion on days 1 and 15 of each 28-day cycle. Manufacturing batch numbers are provided in Section 16.1.6.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Subjects were administered 1000 mg/m^2 of gemcitabine by IV infusion over at least 30 minutes

(± 10 minutes) on days 1, 8, and 15 of each 28-day cycle. Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment: The median length of subject treatment was 5 months.

Study Endpoints:

The primary endpoint was OS. The secondary endpoints were PFS, survival rate at the timepoints of 3, 6, 9, 12, 18, and 24 months, objective response rate, time to disease progression, duration of response, disease control rate (PR+CR+SD); incidence of subject adverse events, laboratory abnormalities and immunogenicity; ganitumab dose exposure, dose intensity and PK parameters; gemcitabine dose exposure, dose intensity and PK parameters; the change in hepatobiliary symptoms using the FACT-Hep HS.

The exploratory endpoints are listed in Section 10.1.3 of the Protocol (Section 16.1.1).

Statistical Methods:

The primary goal of the statistical analysis was to determine if OS in ganitumab 12 mg/kg arm, and/or ganitumab 20 mg/kg arm was statistically significantly improved compared to placebo arm. A log-rank test stratified by the randomization factors was used to compare OS. No adjustment for multiplicity was done due to early stopping of the study futility. Cox proportional hazards regression models was used to provide the 2 OS hazard ratios and 95% confidence interval (CI)s for ganitumab 12 mg/kg or 20 mg/kg in combination with gemcitabine relative to placebo with gemcitabine.

An interim futility analysis of OS was planned when a total of approximately 188 OS events (156 and 118 for the ganitumab 12 mg/kg or 20 mg/kg versus placebo comparison, respectively) were observed. A non-binding stopping boundary using the gamma (0) family (Hwang et al, 1990) suggested stopping the study for futility if the observed hazard ratio was ≥ 0.9871 or 1.003 for the ganitumab 12 or 20 mg/kg arm versus placebo, respectively. The probabilities of meeting the stopping criteria at the interim efficacy analysis under the null and alternative hypotheses for AMG 479 12 mg/kg (20 mg/kg) were 0.532 and 0.030 (0.493 and 0.013), respectively.

Survival rates at the timepoints of 3, 6, 9, and 12 months and the median, 25th and 75th percentiles and their 95% CIs were estimated. The same method was applied to PFS. The proportion of objective response for each treatment arm and difference in proportions and their CIs were estimated. Descriptive summaries of observed data were provided for aggregate scores for the FACT-Hep HS questionnaire at each assessed time point. Descriptive statistics were produced to describe the exposure to ganitumab and gemcitabine by treatment arm. Non-compartment analysis was used to estimate ganitumab and gemcitabine PK parameters. Ganitumab population PK modeling was employed to characterize PK parameters and covariates. Pharmacokinetics simulation was performed to estimate individual patient exposure parameters for exposure-efficacy analyses. Ganitumab exposure-survival relationship was assessed with univariate and multivariate analysis.

Summary of Results: The interim futility analysis was conducted by the DMC after 636 subjects were enrolled and 234 OS events were observed (data cutoff date: 23 April 2012), and the results showed that the futility boundaries were crossed. Therefore, the study was terminated early due to futility. At the time of the interim analysis, 625 (98%) subjects received investigational product and 412 (65%) subjects discontinued the investigational product: 169 (67%), 162 (64%), and 81 (64%) subjects in the placebo, ganitumab 12 mg/kg, and ganitumab 20 mg/kg arms, respectively. The most common reason for discontinuation was disease progression which occurred in 103 (41%), 90 (35%) and 49 (39%) subjects.

Since, higher number of OS events were observed than planned, a revised futility rule using the actual number of events was used, i.e. stopping the study for futility if the observed hazard ratio was ≥ 0.9426 or 0.9443 for the ganitumab 12 or 20 mg/kg arm versus placebo, respectively. The hazard ratios (95% CI) stratified by ECOG were 1.01 (0.76, 1.35) and 1.02 (0.72, 1.46) for the ganitumab 12 or 20 mg/kg arm versus placebo, respectively. Additional HRs stratified for

different possible combination of ECOG, liver metastasis, and region were estimated and regardless of the stratification selected, the HRs all crossed the revised futility boundaries.

The results presented in the rest of this report are based on the final analysis (data cutoff date: 04 April 2013).

Subject Disposition: Eight hundred subjects were randomized in the 2:2:1 ratio; 322, 318 and 160 subjects in the placebo, ganitumab 12 mg/kg, and ganitumab 20 mg/kg arms, respectively. Of those randomized, 99% subjects received at least one dose of investigational product: 98% subjects in the placebo arm, 99% in the ganitumab12 mg/kg arm and 100% subjects in the ganitumab 20 mg/kg arm. Almost all the subjects 99% discontinued the investigational product at some time point; 98%, 99%, 100%. The most common reason was disease progression which occurred in 46%, 42% and 45% of the subjects.

Two hundered- eleven (26%) subjects completed the study: 90 (28%) subjects in the placebo arm, 78 (25%) subjects in the ganitumab12 mg/kg and 43 (27%) subjects in the ganitumab 20 mg/kg arms. Overall, 74% subjects discontinued the study. A total of 64% of the subjects died (63%, 66% and 63% in the placebo, ganitumab12 mg/kg, and ganitumab 20 mg/kg arms, respectively) and 6% subjects discontinued the study due to consent withdrawn (6%, 6% and 7%).

Baseline Demographics:

Sex: Placebo: 58% men; 42% women

Ganitumab 12 mg/kg: 50% men; 50% women

Ganitumab 20 mg/kg: 53% men; 47% women

Age: Placebo: mean (standard deviation [SD]) 62.2 (9.6) years (range: 36 to 83)

Ganitumab 12 mg/kg: mean (SD) 62.1 (9.7) years (range: 36 to 85)

Ganitumab 20 mg/kg: mean (SD) 62.7 (10.1) years (range: 31 to 81)

Ethnicity/Race: Placebo: white: 79%; Asian (Non-Japanese): 11%, black 1%, Japanese 9%, hispanic or latino 0%, other 0%

Ganitumab 12 mg/kg: white: 81%; Asian (Non-Japanese): 6%, Japanese 11%, black 1%, other 1%

Ganitumab 20 mg/kg: white: 81%; Asian (Non-Japanese): 9%, Japanese 10%, other 1%

Efficacy Results:

Overall Survival: A total of 62% of the subjects in the placebo, 66% of the subjects in the ganitumab 12 mg/kg and 63% of the subjects in the ganitumab 20 mg/kg arms reported OS events. The median (95% CI) Kaplan-Meier estimates of OS time in the placebo, ganitumab 12 mg/kg and ganitumab 20 mg/kg arms was 7.2 (6.3, 8.2) months, 7.0 (6.2, 8.5) months, 7.1 (6.4, 8.5) months, respectively. The OS hazard ratio (95% CI) analysed using Cox proportional hazard model, stratified by ECOG performance status and the presence of liver metastases (based on the pooling strategy as detailed in Section 10.5 of the SAP) was 1.00 (0.82, 1.21) and 0.97 (0.76;1.23) for ganitumab 12 mg/kg and 20 mg/kg arms, respectively.

Progression Free Survival: A total of 75% of the subjects in the placebo, 76% of the subjects in the ganitumab 12 mg/kg and 68% of the subjects in the ganitumab 20 mg/kg arms reported OS events (progression or death). The median (95% CI) Kaplan-Meier estimates of PFS time in the placebo, ganitumab 12 mg/kg and ganitumab 20 mg/kg arms was 3.7 (3.6, 4.4) months, 3.6 (3.4, 3.8) months and 3.7 (3.2, 5.0) months, respectively. The hazard ratio (95% CI) analysed by Cox proportional hazard model and stratified by ECOG performance status and the presence of liver metastases was 1.00 (0.84, 1.20) and 0.97 (0.77;1.22) for ganitumab 12 mg/kg and 20 mg/kg arms, respectively.

Objective Response: The percentage (95% CI) of objective responders was 10.2% (7.08, 14.08), 16.1% (12.13, 20.68) and 14.7% (9.43, 21.36) in the placebo, ganitumab 12 mg/kg and ganitumab 20 mg/kg arms, respectively. The difference in the response rates (95% CI) for

ganitumab 12 mg/kg and 20 mg/kg was 5.87 (95% CI: 0.31, 11.47) and 4.48 (-1.98, 12.02), relative to placebo.

The 3 assayed biomarkers [redacted] failed to identify an enriched population with a stronger treatment effect on OS. Similar hazard ratios for ganitumab (12mg/kg or 20mg/kg) vs. placebo were observed by biomarker subgroups (below vs. above median). For the 3 biomarkers, no significant interaction between biomarker expression (below vs. above median) and treatment (12mg/kg ganitumab vs. placebo or 20mg/kg ganitumab vs. placebo) were observed. The conclusion was the same for PFS.

Other Evaluations:

Pharmacokinetics and Exposure-Efficacy Analyses:

Ganitumab PK: The estimated mean (SD) clearance was 12.7 (3.9) and 12.9 (3.0) mL/day/kg for the 12 and 20 mg/kg arms, respectively, indicating linear kinetics in the dose range. The steady state area under the curve $(AUC)_{tau}$ increased by 1.6-fold when dose was increased from 12 to 20 mg/kg (1.7 fold). The accumulation ratio of ganitumab area under curve (AUC) between the first dose and the third dose (steady state) was up to 1.2 fold under the every other week regimen. The PK linearity was not affected by the coadministration of ganitumab with gemcitabine.

Gemcitabine PK: The gemcitabine steady state mean (SD) AUC_{24} levels in the placebo, ganitumab12 mg/kg and 20 mg/kg arms were 9.98 (4.19), 9.00 (4.47), and 9.48 (3.97) µg•hr/mL, respectively); and the AUC_{24} value of gemcitabine metabolite 2' deoxy-2',2'-difluorouridine was 249 (68.5), 249 (48.7), 261 (48.6) µg•hr/mL, respectively) indicating there was no observed effect of ganitumab co-administration on the gemcitabine PK.

Ganitumab Population PK Modeling: A linear two-compartment model adequately described ganitumab concentration data. The estimated typical value of ganitumab clearance and volume of distribution in the central compartment was 0.0407 L/hr and 4.06 L, respectively, in pancreatic cancer patients. Pancreatic cancer patients showed approximately 1.5 fold higher clearance than that of non-pancreatic cancer patients. Covariate analysis suggested that body weight, baseline albumin, creatinine clearance, alkaline phosphatase, neutrophil levels, ECOG score and sex affect the ganitumab PK.

Ganitumab Exposure-Efficacy Analyses: Steady state area under curve (AUC_{ss}) was used as a ganitumab exposure parameter, and PFS and OS were used as survival measures. In the univariate analysis, higher ganitumab exposure appeared to associate with longer survival. However, it was found in the multivariate analysis, the baseline prognostic factors including alkaline phosphatase, albumin, tumor size, liver metastasis, ECOG and shift in blood glucose from baseline played major roles in OS, while ganitumab AUC_{ss} was an insignificant factor affecting OS.

Patient-reported Outcome: For the FACT-Hep HS, the number of subjects who received treatment and the compliance of those subjects with completing the questionnaire were similar among the treatment arms. All 3 treatment arms were similar at baseline and did not demonstrate any pronounced differences in compliance during the course of the study.

Total score was balanced between arms at baseline and there was no significant difference between the treatment arms; addition of ganitumab was not associated with a change in quality of life score. By cycle 5, the mean change from baseline was -1.68 (SD 9.19) for subjects in the placebo arm and 0.81 (SD 9.97) and -0.78 (SD 10.85) in the 12 and 20 mg/kg ganitumab arms, respectively. Additionally, the number of subjects completing the questionnaire decreased in compliance.

Antiganitumab antibodies: Six (3%) subjects from the placebo arm and no subjects from the ganitumab arms tested positive for antiganitumab binding antibodies post treatment. No subjects tested positive for neutralizing antibodies.

Safety Results: Treatment-emergent adverse events were reported for 98%, 98%, 99% subjects in the placebo arm, ganitumab 12 mg/kg, and ganitumab 20 mg/kg, respectively. Similar proportions of subjects experienced fatal adverse events (10%, 10%, and 11%). The proportions

were also similar for serious adverse events (44%, 41%, and 43%). Adverse events with a worst grade of 3 or 4 occurred in 56%, 68%, and 59% subjects. Few subjects discontinued the study due to adverse events in any treatment arm (2%, 1%, 1%, in the placebo arms, ganitumab 12 mg/kg, and ganitumab 20 mg/kg, respectively). The most common adverse events (those occurring in ≥ 30% of all subjects combined) were nausea (40%,42%, and 44% subjects in the placebo arms, ganitumab 12 mg/kg, and ganitumab 20 mg/kg, respectively); neutropenia (34%,37%, and 33%); thrombocytopenia (30%,40%, and 34%); and fatigue (29%,35%, and 39%).

Adverse events leading to discontinuation of investigational product occurred in 19%, 24%, and 18% subjects in the placebo, ganitumab12 mg/kg, and ganitumab 20 mg/kg, respectively. The most common (occurring in ≥ 3% of subjects), were increased alanine aminotransferase (3%, 5%, and 2%) and increased aspartate aminotransferase (2%, 4%, and 3%).

Grade 3 and 4 adverse events of interest were drug related hepatic disorder (6% subjects in the placebo arm,7% subjects in the ganitumab 12 mg/kg arm and 4% subjects in the ganitumab 20 mg/kg arm), venous thrombotic events (3%, 5% and 3%), hyperglycaemia (3%, 14%, 19%), infusion reactions (0%, 1%, 1%), neutropenia (24%, 27%, 22%), rash (0%, 1%, 1%) and thrombocytopenia (8%, 10%, 8%).

Overall, hematology and chemistry laboratory abnormalities were similar for the placebo and ganitumab arms except for alanine aminotransferase, glucose, and sodium. For these 3 analytes, the subject incidence of ≥ grade 3 maximum laboratory toxicities was at least 5% higher in 1 or both ganitumab arms relative to the placebo arm. Twenty six (8.0%) subjects in the placebo arm and 112 (24.0%) subjects in the ganitumab (combined) arm reported ≥ grade 3 increase in glucose. Thirty three (10.0%) subjects in the placebo arm and 69 (15.0%) subjects in the ganitumab (combined) arm reported ≥ grade 3 increase in the alanine aminotransferase. Related adverse events were reported in small numbers of subjects.

Conclusions: Based on the data observed at pre-planned interim analysis by the DMC, the study was terminated early due to futility. Data from final analysis presented here showed that addition of ganitumab to gemcitabine did not improve OS or PFS for the treatment of metastatic adenocarcinoma of the pancreas compared to gemcitabine alone. The safety profile was consistent with the safety profile of ganitumab available to date. No antiganitumab neutralizing antibodies developed in any subject, and no new safety concerns were observed.

The ganitumab PK in pancreatic cancer patients was linear and did not appear to be affected by the co-administration of gemcitabine. The gemcitabine PK did not appear to be affected by the co-administration of ganitumab. Population PK analysis suggested that pancreatic cancer patients appeared to have higher ganitumab clearance and lower exposure than that in non-pancreatic cancer patients at a given dose. Exposure-survival analysis did not show that ganitumab AUCss was a significant factor affecting the survival profile.