SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: ganitumab (AMG 479)

Name of Active Ingredient: ganitumab

Title of Study: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Trial of AMG 479 or Placebo in Combination with Gemcitabine as First-line Therapy for Locally Advanced Unresectable Adenocarcinoma of the Pancreas

Investigators and Study Centers: This study was conducted at 9 centers in 7 countries. Centers and principal investigators are listed in Appendix 2.

Publications: None

Study Period: 31 May 2012 (first subject enrolled) to 27 November 2012 (last subject visit). This study was terminated early (09 August 2012) due to the early termination of a trial in a similar tumor population (Study 20060540: a, phase 3 trial of ganitumab in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas).

Development Phase: 2

Objectives:

The primary objective of this study was to estimate the relative treatment effect of ganitumab in combination with gemcitabine compared with placebo in combination with gemcitabine as measured by the hazard ratio for progression-free survival (PFS) in subjects with locally advanced adenocarcinoma of the pancreas.

The secondary objectives were:

- to evaluate overall survival (OS)
- to evaluate the PFS and OS rates at 3, 6, 9, 12, 18, and 24 months
- to evaluate objective response rate, time to progression, duration of response, and disease control rate (partial response [PR] + complete response [CR] + stable disease [SD]) as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- to evaluate subject incidence of adverse events, significant laboratory abnormalities, and immunogenicity
- to evaluate ganitumab dose intensity, dose exposure and pharmacokinetic (PK) parameters, and to evaluate relationships between ganitumab exposure measures and selected safety and efficacy measures
- to evaluate gemcitabine dose intensity and dose exposure
- to evaluate patient reported outcomes as measured by the FACT Hepatobiliary Questionnaire – Hepatobiliary subscale (FACT-Hep HS)
- to evaluate outcomes (PFS and OS) with respect to biomarker enrichment status defined by an analysis of serum biomarkers in metastatic pancreatic cancer (Study 20060540)

Exploratory objectives are provided in the protocol (Section 1.3, Appendix 1).

Methodology:

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, two-arm study. Subjects were randomized in a 1:1 ratio to receive ganitumab plus gemcitabine (arm 1) or ganitumab-placebo (placebo) plus gemcitabine (arm 2). Gemcitabine (1000 mg/m^2) was administered by intravenous (IV) infusion on days 1, 8, and 15 of a 28-day cycle followed by ganitumab (20 mg/kg) or placebo IV infusion on days 1 and 15.

Subjects were administered protocol-specified therapy until disease progression per RECIST version 1.1, unacceptable toxicities, withdrawal of consent, or start of a new systemic anti-cancer therapy.

Subjects were evaluated for tumor response using radiographic imaging at week 8 (± 7 days) and every 8 weeks (± 7 days) independent of the treatment cycle until disease progression or withdrawal of consent, regardless of the initiation of a new systemic anti-cancer therapy.

Safety was assessed by determining the nature, frequency, severity, relation to treatment and outcome of all adverse events, changes in laboratory safety variables and vital signs, and formation of antibody to the investigational product. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.

All subjects were assessed for safety at a 30 day (+3 days) safety follow-up visit after the last dose of protocol-specified therapy. Subjects who discontinued protocol-specified therapy 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) until withdrawal of consent or the end of the study.

Full details of the methodology for this study are provided in the protocol (Appendix 1).

This study was terminated early based on results of a pre-planned interim analysis conducted during a phase 3 trial of ganitumab in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas (Study 20060540). The data monitoring committee for Study 20060540 determined that the combination of ganitumab with gemcitabine was unlikely to demonstrate a statistically significant improvement in the primary endpoint of OS compared with gemcitabine alone. Results for Study 20080261 are presented as a synopsis because of the small number of subjects randomized, their low exposure to ganitumab, and the futility of demonstrating a significant improvement in OS in Study 20060540 and its early termination.

Number of Subjects Planned: Approximately 150 subjects

Diagnosis and Main Criteria for Eligibility: Subjects included men and women ≥ 18 years of age, with histologically or cytologically confirmed locally advanced adenocarcinoma of the pancreas that was unresectable per institutional practice; radiologically measurable and/or non-measurable disease as defined by RECIST version 1.1; and Eastern Cooperative Oncology Group performance status score of 0 or 1. Additional eligibility criteria are provided in the protocol (Section 4, Appendix 1).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Subjects were administered 20 mg/kg of ganitumab and ganitumab-placebo by IV infusion on days 1 and 15 of each 28-day cycle. The manufacturing batch number for ganitumab and ganitumab-placebo was [redacted].

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. The manufacturing batch number for gemcitabine was [redacted].

Duration of Treatment: Ganitumab or placebo was administered by IV infusion after completion of the gemcitabine IV infusion until radiographic disease progression, unacceptable toxicities, withdrawal of consent, or start of a new systemic anti-cancer therapy. The estimated median length of subject treatment was 5 months.

Study Endpoints:

The primary endpoint was PFS.

The secondary endpoints were:

- OS
- PFS and OS rates at 3, 6, 9, 12, 18, and 24 months

- objective response rate: defined as the incidence rate of either a CR or PR (per RECIST version 1.1)
- time to disease progression: defined as time from the date of randomization to disease progression (per RECIST v1.1)
- duration of response: defined as time from the date of first response (PR or CR) to disease progression (per RECIST v1.1) or death
- disease control rate: defined as the incidence rate of either a CR, or PR, or SD (per RECIST version 1.1)
- incidence of subjects adverse events, laboratory abnormalities and immunogenicity
- ganitumab dose intensity, dose exposure and PK parameters
- gemcitabine dose intensity and dose exposure
- relationship between ganitumab exposure measures and selected safety and efficacy measures
- the area under the curve for the hepatobiliary symptoms subscale as measured by the FACT-Hep HS

Statistical Methods:

A Cox proportional hazards regression model stratified by the randomization factor was to be used to estimate the PFS hazard ratios and two-sided 80% and 95% confidence intervals for ganitumab plus gemcitabine relative to placebo plus gemcitabine. Details for analysis of this primary efficacy endpoint and the secondary efficacy endpoints are provided in the protocol (Section 10.5, Appendix 1).

The subject incidence of all treatment-emergent adverse events was to be summarized for each treatment arm by system organ class and preferred term and was to be further classified by relationship to treatment. Laboratory safety data was to be tabulated and summarized at each scheduled time point in the study.

Due to the small number of subjects, low treatment exposure, and short duration of follow-up, the data were not analyzed as planned. Listings were produced for demographic and baseline characteristics, important protocol deviations, PFS, OS, tumor response, treatment exposure, binding and neutralizing antibody, and deaths. In addition, the subject incidence of adverse events was summarized by worst grade and preferred term; the subject incidence of grade 3 or higher toxicity for laboratory parameters was summarized.

Summary of Results:

Subject Disposition:

Ten subjects were enrolled in the study. Eight subjects were administered protocol-specified treatment; 3 subjects were administered ganitumab in combination with gemcitabine and 5 subjects were administered placebo in combination with gemcitabine. Of the 2 subjects who did not receive study treatment; 1 (Subject [redacted]) did not meet inclusion criteria and 1 (Subject [redacted]) withdrew full consent.

Important protocol deviations were reported for 2 subjects. Both subjects entered the study even though all entry criteria was not satisfied. Subject [redacted] had laboratory results for partial thromboplastin time and international normalized ratio that were not confirmed within 14 days of the first dose of study treatment and had alanine amino transferase levels outside the normal range 3 days before the first dose of protocol-specified treatment. Subject [redacted] had metastatic (Stage IV) disease rather than locally advanced disease during screening for the current malignancy (Listing 14-3.1).

Subject Demographics:

Sex: [redacted]

Age: [redacted]

Ethnicity (Race): [redacted]

Other subject demographics and baseline characteristics are provided in Listing 14-2.1 and Listing 14-2.2.

Efficacy Results:

Data were not analyzed as planned due to the early termination of the study and the small number of subjects randomized into the study. Progression-free survival time, OS time, and tumor response by time point were listed for each subject.

A listing of PFS time for the full analysis set (all randomized subjects) is presented in Listing 14-4.3. Two subjects [redacted] from the placebo plus gemcitabine arm exhibited disease progression at day 48 and 58, respectively.

A listing of OS time for the full analysis set is presented in Listing 14-4.3. The OS data was not mature as 9 out of 10 subjects were censored. One subject [redacted] from the placebo plus gemcitabine arm died on day 99.

A listing of tumor response by time point (weeks 8 and 16) is presented in Listing 14-4.2. Two subjects were not assessed for tumor response as they withdrew from the study before receiving treatment and did not have a post baseline scan. At week 8, 5 subjects had SD. Two subjects exhibited disease progression and 1 subject had non-progressive disease. At week 16, 2 subjects had SD and 1 subject had non-progressive disease; no week 16 results were available for the other 5 subjects. No scans were performed beyond week 16.

Safety Results:

Exposure to protocol-specified treatment by cycle is presented in Listing 14-5.1. Eight of 10 subjects received at least 1 dose of protocol-specified treatment. The following 3 subjects received ganitumab:

- Subject [redacted] received 1 dose of ganitumab after which subject was hospitalized due to an adverse event (hepatic hematoma); dosing was withheld. The subject did not receive another dose of ganitumab due to Amgen`s decision to stop the study.
- Subject [redacted] received ganitumab at C1D1 and discontinued ganitumab on day 15, due to Amgen`s decision after the release of futility analysis from Study 20060540.
- Subject [redacted] received 3 doses ganitumab at C1D1, C1D15, and C2D1, and discontinued ganitumab after the release of futility analysis from Study 20060540.

A summary of the subject incidence of treatment-emergent adverse events is presented in Table 14-6.1. All 8 subjects included in the Safety Analysis Set experienced at least 1 adverse event (3 subjects were in the ganitumab plus gemcitabine arm and 5 subjects were in the placebo plus gemcitabine arm). One subject [redacted], a [redacted], died approximately 2.5 months after [redacted] last dose of placebo plus gemcitabine. The primary cause of death was progression of disease (Listing 14-8.1).

Overall, the most frequently experienced adverse events were anemia (5 subjects [63%]), fatigue (4 subjects [50%]), and neutropenia (3 subjects [38%]). In the ganitumab plus gemcitabine arm, the most frequently experienced adverse events were anemia (3 subjects [100%]) and neutropenia and thrombocytopenia (2 subjects [67%] each). In the placebo plus gemcitabine arm, the most frequently experienced adverse events were fatigue (3 subjects [60%]), and anemia, decreased appetite, diarrhea, and pyrexia (2 subjects [40%] each). All other adverse events occurred in 1 subject (Table 14-6.1).

Overall, 4 subjects (50%) experienced treatment-emergent grade 3 or 4 adverse events (Table 14-6.2). Three of these subjects experienced grade 3 and 1 subject experienced grade 4

adverse events. Grade 3 anemia was reported for 3 subjects (38%); 2 of these subjects were administered ganitumab plus gemcitabine and 1 subject was administered placebo plus gemcitabine. A grade 4 decrease in blood potassium was reported for 1 subject who received ganitumab plus gemcitabine.

Three subjects experienced serious adverse events (Listing 14-6.3); 2 of these subjects were administered ganitumab plus gemcitabine and 1 subject was administered placebo plus gemcitabine. Subject [redacted] who was administered ganitumab plus gemcitabine experienced oesophageal candidiasis and hepatic hematoma; both events were grade 3 in severity. Only the hepatic hematoma was considered to be treatment-related. Subject [redacted] who was administered ganitumab plus gemcitabine experienced 2 events of anemia which were grade 3 in severity and considered serious. The first event of anemia was considered to be related to gemcitabine; the second event was not considered to be treatment-related. Subject [redacted] who was administered placebo plus gemcitabine experienced general physical health deterioration (twice) and malaise. The event of malaise was considered to be related to placebo plus gemcitabine. Narratives for subjects with serious adverse events are provided in Appendix 5.

The subject incidence of CTCAE grade 3 or higher toxicities in laboratory parameters is presented by treatment arm in Table 14-7.1. Two subjects (1 in each treatment arm) had grade 3 toxicities of sodium and hemoglobin. No more than 1 subject had a grade 3 or higher toxicity for any other laboratory parameters.

No subject tested positive for anti-ganitumab binding antibodies (Listing 14-8.2).

Conclusions:

Because of the early termination of this study and the small number of subjects that were enrolled, no conclusions regarding efficacy or safety can be made.