2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Romiplostim

Name of Active Ingredient: Romiplostim

Title of Study: Phase 2, Randomized, Double Blind, Placebo-Controlled Dose and Schedule Finding Trial to Evaluate the Safety and Efficacy of AMG 531 for Treatment of Chemotherapy-Induced Thrombocytopenia in Subjects With Advanced Non-Small Cell Lung Cancer Already Receiving Gemcitabine and Platinum

Investigators and Study Centers: This study was conducted at 24 centers in North America and Europe (Appendix 4).

Publications: None

Study Period: First subject enrolled 28 December 2006; last subject completed study 02 December 2009.

Development Phase: 2

Introduction and Objectives:

Romiplostim (AMG 531) is an Fc fusion protein (peptibody) that increases platelet production via the thrombopoietin (TPO) receptor, which signals and activates transcriptional pathways. Romiplostim has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Romiplostim is produced in E coli by recombinant DNA technology. Romiplostim is engineered by fusing an IgG1 Fc domain to 2 copies of a synthetic 14-residue thrombopoietin receptor (c-Mpl) binding domain. The approximate molecular weight is 59 kilodaltons.

Romiplostim has been shown to increase platelet counts in healthy human subjects and in subjects with immune (idiopathic) thrombocytopenic purpura (ITP). The primary objective of the current study was to evaluate the safety of romiplostim in treating chemotherapy-induced thrombocytopenia (CIT) in subjects with non-small cell lung cancer (NSCLC) receiving myelosuppressive chemotherapy. The secondary objective was to evaluate the efficacy of romiplostim (dose and schedule) in treating CIT in subjects with NSCLC receiving myelosuppressive chemotherapy.

Methodology:

This randomized, double-blind, placebo-controlled, sequential dose-escalation cohort study was designed to identify a well tolerated, effective dose and schedule of romiplostim in subjects with NSCLC who had already experienced thrombocytopenia during the chemotherapy cycle immediately preceding study entry. Subjects with stage IIIB or stage IV NSCLC receiving chemotherapy with 21-day cycles of gemcitabine/carboplatin or gemcitabine/cisplatin were appropriate to screen for this study. Eligible subjects must have experienced thrombocytopenia as a result of chemotherapy administered in a qualifying cycle immediately preceding study entry and must have recovered to a platelet count of at least 100 x 10^9/L by day 1 of the first on-study treatment cycle.

Eligible subjects were randomly assigned to either romiplostim or placebo in 1 of 3 sequential dose-escalation cohorts: 250, 500, and 750 µg. Within each dose cohort, subjects were allocated to romiplostim or placebo in a ratio of 4:1. Subjects received 1 subcutaneous (SC) administration of investigational product per chemotherapy cycle (up to 5 cycles total). Subjects were to receive the same dose and schedule of chemotherapy during the first on-study treatment cycle as during the prior qualifying cycle (except for label-required modification to the dose or timing of the day 8 gemcitabine). Subjects continued to receive investigational product in all remaining chemotherapy cycles at the same dose and schedule to which they were originally assigned. All chemotherapy administered after the first on-study cycle was administered at the discretion of the investigator with regard to dose, schedule, and timing of administration. In addition, platelet transfusions were allowed if necessary and were administered according to the American Society of Clinical Oncology guidelines or the Guidelines for the Use of Platelet Transfusions.

A data review team (DRT) monitored ongoing safety and efficacy and made recommendations about the progress of the study. The DRT reviewed the unblinded study data in each cohort after all subjects in the cohort completed their first on-study treatment cycle. The DRT could recommend dose escalation, additional dose and schedule cohorts, the expansion of cohorts, or the stopping of the study. The DRT made dose-escalation recommendations based on a benefit/risk assessment of the occurrence of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) v3.0 grade 3 or 4 treatment-related adverse events for each cohort. The DRT could recommend intermediate doses in units of 250 µg up to a maximum dose of 1500 µg.

Number of Subjects Planned: A total of 45 subjects (15 per dose cohort) were planned for inclusion in this study. Additional confirmatory dose and schedule cohorts could be considered for a maximum of 95 subjects.

Number of Subjects Enrolled: 63

Sex: 45 male, 18 female

Age: Mean (SD) years of age in the placebo, 250-µg, 500-µg, and 750-µg groups were 59.8 (6.6), 63.8 (10.8), 62.5 (7.7), and 65.4 (8.2), respectively.

Ethnicity (Race): 62 white, 1 black

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria:

- Histologically or cytologically confirmed locally advanced or metastatic stage IIIB (not amenable to surgery or radiotherapy with a curable intent) or stage IV NSCLC
- Receiving chemotherapy with 21-day cycles of gemcitabine/carboplatin or gemcitabine/cisplatin
- Life expectancy ≥ 12 weeks at the time of screening
- Thrombocytopenia as evidenced by a platelet count $\leq 50 \times 10^9$/L during the qualifying cycle of chemotherapy, OR platelet count $< 100 \times 10^9$/L on day 22 of the qualifying cycle
- Ability to receive the same dose and schedule of chemotherapy during the first on-study treatment cycle as was given in the qualifying cycle (except day 8 gemcitabine)
- Absolute neutrophil count (ANC) ≥ 1,000/µL, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L on day 1 of the first on-study chemotherapy treatment cycle
- ≥ 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 at the time of screening

- Adequate liver function: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3.0 x upper limit of normal (ULN) (except for subjects with liver metastases, who could have AST and ALT ≤ 5 x ULN); and serum bilirubin ≤ 1.5 x ULN (except for subjects with a confirmed diagnosis of Gilbert's Syndrome)
- Adequate renal function: serum creatinine < 1.5 x ULN
- Provided appropriate written informed consent

Exclusion Criteria:

- Receipt of > 1 prior systemic chemotherapy regimen
- Sepsis, disseminated intravascular coagulation, or any other condition (ie, ITP, thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS]) that may have exacerbated thrombocytopenia
- History of unstable angina, chronic heart failure (New York Heart Association > class II), uncontrolled hypertension (diastolic > 100 mm Hg), uncontrolled cardiac arrhythmia, or recent (within the last 1 year before screening) myocardial infarction
- History of arterial thrombosis (eg, stroke or transient ischemic attack) within the last 1 year before screening
- History of pulmonary embolism or other venous thrombosis within the last 1 year before screening (except for catheter-related clots)
- Receipt of any nitrosourea (carmustine [BCNU], lomustine [CCNU]) or mitomycin C within the last 6 weeks before screening
- Receipt of any thrombopoietic growth factor or related substance
- Receipt of granulocyte-macrophage colony-stimulating factor (GM-CSF) within the last 4 weeks before screening
- Receipt of any experimental therapy within the last 4 weeks before screening
- Receipt of a bone marrow or peripheral blood stem cell infusion within the last 1 year before screening
- Pregnant or breast feeding
- Reproductive potential and not using adequate contraceptive precautions in the judgment of the investigator
- Hypersensitivity to any recombinant E coli-derived product
- Inability to comply with the protocol

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Romiplostim was provided as a sterile, white, preservative-free, lyophilized powder in 5.0 mL single-use glass vials such that, after reconstitution with [redacted] mL of sterile water for injection, romiplostim concentration 0.5 mg/mL [redacted]. Romiplostim was administered by SC injection at doses of 250, 500, or 750 μg on the first day after chemotherapy for up to a maximum of 5 chemotherapy cycles. Romiplostim manufacturing batch numbers [redacted], [redacted], [redacted], [redacted], and [redacted] were used for this study.

Duration of Treatment: The number of chemotherapy treatment cycles was planned individually for each subject (up to a maximum of 5 cycles), and the subjects were to receive investigational product on day 2 of each of their cycles.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo was provided as a lyophilized powder in 5.0 mL single-use glass vials such that, after reconstitution with [redacted] mL of sterile water for injection, the vials contained [redacted].. Placebo was administered by SC injection at doses volume-matched to romiplostim doses within each cohort on the first day after chemotherapy for up to a maximum of 5 chemotherapy cycles. Placebo manufacturing batch numbers [redacted], [redacted], and [redacted] were used for this study.

Study Endpoints:

Primary Endpoint:

Incidence of adverse events, including the incidence of anti-romiplostim antibody formation

Secondary Endpoints:

- Incidence of subjects who experience grade 3 or 4 thrombocytopenia (< 50 x 10^9/L) during the first on-study chemotherapy treatment cycle
- Duration of grade 3 or 4 thrombocytopenia experienced during the first on-study chemotherapy treatment cycle
- Platelet count on day 22 of the first on-study chemotherapy treatment cycle (planned day 1 of the next cycle)
- Incidence of subjects who are administered platelet transfusions during the first on-study chemotherapy treatment cycle
- Incidence of subjects who require gemcitabine dose reduction on day 8 of the first on-study chemotherapy treatment cycle

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Statistical Methods:

Descriptive statistics were used to evaluate the primary and secondary efficacy endpoints. Point estimates, along with 2-sided 95% confidence intervals (CIs), were presented for primary and secondary endpoints. Descriptive statistics included the number of subjects, mean, median, standard deviation, 25th and 75th percentiles, minimum, and maximum for continuous variables; and frequencies and percentages for categorical variables.

Tests of statistical significance were performed on some efficacy endpoints by comparing the result in the pooled placebo group to that in each romiplostim dose group. Fisher's exact test was used to compare subject incidences for the following endpoints: grade 3 or 4 thrombocytopenia during the first treatment cycle; platelet transfusions during the first treatment cycle; and gemcitabine dose reduction on day 8 of the first treatment cycle. Both Satterthwaite t-test and Wilcoxon rank-sum test were used to compare the following endpoints: duration of grade 3 or 4 thrombocytopenia during the first treatment cycle; platelet count on day 22 of the first treatment cycle; and time for platelet count to recover to 100 x 10^9/L from nadir or from day 1 in the first treatment cycle.

The subject incidence of adverse events was summarized for each treatment group by system organ class and by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). This summary included all treatment-emergent adverse events recorded from the start of investigational product on this study or any worsening of adverse events initially experienced before initiation of this study.

Summary of Results:

Subject Disposition:

A total of 63 subjects were randomized to the study, 62 (98%) received study treatment and were analyzed for safety, and 61 (97%) completed at least 1 on-study treatment cycle and were analyzed for efficacy.

Of the 50 subjects who received romiplostim at doses of 250 µg (n = 16), 500 µg (n = 18), or 750 µg (n = 16), 81%, 89%, and 77%, respectively, completed study. Of the 12 subjects who received placebo, 11 (92%) completed study.

Safety Results:

As would be expected in this patient population, adverse events were reported for most subjects: 12/12 (100%) in the placebo group, 16/16 (100%) in the 250-µg group, 18/18 (100%) in the 500-µg group, and 14/16 (88%) in the 750-µg group (48/50 [96%] in the romiplostim dose groups combined).

Subject incidences of serious adverse events in the placebo, 250-µg, 500-µg, and 750-µg groups were 1/12 (8%), 7/16 (44%), 5/18 (28%), and 5/16 (31%), respectively. None of the serious adverse events were reported as related to investigational product. Two subjects died on study: 1 subject in the 500-µg group (hypotension/bronchopneumonia/sepsis/heart attack) and 1 subject in the 750-µg group (progressive NSCLC); both deaths were considered by the investigator to have been unrelated to investigational product. Two subjects discontinued study and/or investigational product early due to adverse events: 1 subject in the 750-µg group (thrombocytopenia; reported as not related to investigational product) and 1 subject in the 500-µg group (increased platelet count; reported as related to investigational product). The subject incidences of adverse events reported as ≥ CTCAE v3.0 grade 3 in severity in the placebo, 250-µg, 500-µg, and 750-µg groups were 4/12 (33%), 10/16 (63%), 11/18 (61%), and 9/16 (56%), respectively (30/50 [60%] for the romiplostim dose groups combined); none of these events were considered related to investigational product.

Adverse events identified as adverse events of interest, and the corresponding subject incidences (placebo group, combined romiplostim groups) were: haemorrhage adverse events (0/12 [0%], 5/50 [10%]); embolic or thrombotic adverse events (0/12 [0%], 3/50 [6%]); malignancy adverse events (0/12 [0%], 0/50 [0%]); renal impairment adverse events (0/12 [0%], 5/50 [10%]); thrombocytosis adverse events (0/12 [0%], 2/50 [4%]); immunogenicity adverse events (none); medication error adverse events (none); and off-label use adverse events (none).

Overall, adverse events were reported as treatment related in the placebo, 250-µg, 500-µg, and 750-µg groups for 0/12 (0%), 2/16 (13%), 1/18 (6%), and 0/16 (0%) subjects, respectively (3/50 [6%] subjects in the romiplostim dose groups combined). No adverse event was reported as treatment related for > 1 subject in any treatment group. All treatment-related adverse events were reported as mild or moderate in severity.

There was no evidence of clinically significant adverse effects of romiplostim on mean laboratory values for hepatic function, renal function, or nonhematologic clinical laboratory parameters; or for vital signs or physical findings. Changes in hematologic clinical laboratory parameters were consistent with the known hematologic toxicities of the chemotherapy regimens and, in the case of platelet counts, with expected pharmacologic effects of romiplostim.

No anti-romiplostim or anti-TPO neutralizing antibodies were detected in any subjects.

Efficacy Results:

The romiplostim groups were not significantly different from the placebo group for any efficacy endpoints (secondary and exploratory endpoints), including subject incidence or duration of grade 3 or 4 thrombocytopenia (< 50 x 10^9/L) during the first treatment cycle, platelet count on day 22 of the first cycle, time for platelet count to recover to 100 x 10^9/L from nadir or from day 1 in the first cycle, subject incidence of platelet transfusion during the first cycle, and subject incidence of gemcitabine dose reduction on day 8 of the first cycle. Other exploratory efficacy results also were similar between the romiplostim groups and the placebo group.

Because a higher proportion of subjects received the carboplatin-containing regimen (more likely than cisplatin to cause severe thrombocytopenia) in the romiplostim groups (33/49 [67%]) than in the placebo group (2/12 [17%]), ad hoc subgroup analyses were undertaken. Among all subjects receiving a cisplatin-containing regimen (N = 27 [10 placebo, 17 romiplostim], median platelet counts after approximately day 12 of treatment cycle 1 were higher for subjects receiving romiplostim than for subjects receiving placebo. (A similar ad hoc analysis for subjects receiving the carboplatin-containing regimen was not done because only 2 subjects in the placebo group received this regimen.)

Conclusions: A single dose of romiplostim 250, 500, or 750 µg once with each chemotherapy treatment cycle was tolerable in this phase 2, dose-finding study in subjects with NSCLC and CIT. At the doses and schedules studied, romiplostim did not demonstrate significant effects on any of the efficacy measures in the study, including platelet counts or numbers of platelet transfusions. Imbalance in the chemotherapy regimens received between the romiplostim and placebo groups limit the efficacy conclusions from this exploratory study.