2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: Romiplostim (formerly AMG 531)

Title of Study: An Open Label Extension Study Evaluating the Safety of Long Term Dosing of Romiplostim in Thrombocytopenic Subjects with Myelodysplastic Syndromes (MDS)

Investigator(s) and Study Center(s): This study was conducted at 43 centers in 13 countries. Principal Investigators are listed in Appendix 4.

Publication(s):

Fenaux P, Kantarjian HM, Muus P, et al. Update of An Open-Label Extension Study Evaluating the Long-Term Safety and Efficacy of Romiplostim in Thrombocytopenic Patients with Myelodysplastic Syndromes (MDS) [abstract]. *Blood* (ASH Annual Meeting Abstracts). 2011;118:1193-1194. Abstract 2772.

Fenaux P, Kantarjian H, Lyons RM, et al. Update from an Open-Label Extension Study Evaluating the Long-Term Safety and Efficacy of Romiplostim In Thrombocytopenic Patients (Pts) with Myelodysplastic Syndromes (MDS) [abstract]. *Blood* (ASH Annual Meeting Abstracts). 2010;116:786. Abstract 1885.

Fenaux P, Kantarjian H, Lyons R et al. An Open-Label Extension Study Evaluating the Long-Term Safety and Efficacy of Romiplostim in Thrombocytopenic Patients (Pts) with Myelodysplastic Syndromes (MDS) [abstract]. *Blood* (ASH Annual Meeting Abstracts). 2009;114:1081. Abstract 2765.

Fenaux, P, Kantarjian H, Lyons RM et al. Update of open-label extension study evaluating the long-term safety and efficacy of romiplostim in thrombocytopenic patients with myelodysplastic syndromes (MDS). *Leuk Res.* 2011;35(suppl 1):S84.

Study Period: 54 months *(*first subject enrolled to last subject completed long-term follow-up)

Development Phase: Open-label extension

Objectives:

Primary Objective: To provide long-term safety data for the use of romiplostim in thrombocytopenic subjects with MDS

Secondary Objective(s): To evaluate the effectiveness of romiplostim with respect to platelet response, transfusion, and bleeding events in the treatment of thrombocytopenic subjects with MDS.

Methodology:

This was an open-label extension study designed to assess the safety of romiplostim for the treatment of thrombocytopenia (platelet count ≤ 50 x 10^9/L) in MDS subjects.

Number of Subjects Planned: Approximately 250.

Number of Subjects Enrolled: 72

Diagnosis and Main Criteria for Eligibility:

This study was available to subjects who completed a previous romiplostim study for the treatment of thrombocytopenia in subjects with low or intermediate-1 risk MDS. Key inclusion criteria included a platelet count of ≤ 50 x 10^9/L since the final dose of romiplostim in the parent study, demonstrating a medical need for continued therapy. Subjects with disease progression to a higher risk disease category or acute myeloid leukemia (AML) in the parent study or with a blast count ≥ 10% by peripheral blood or bone marrow biopsy at screening were not eligible for enrollment.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Romiplostim was administered by subcutaneous injection. All subjects rolling over from an open-label study remained on the same dosing schedule as in the parent study but were reassigned to the closest dose among the dose options allowed for in the current study. All subjects rolling over from a blinded study began at 750 µg weekly on the current study unless a dose reduction or dose increase was required per parent study algorithm. If a dose reduction was required on the blinded parent study, the dose and schedule on the current study remained the same as the final dose on the parent study. If a dose increase was required on the blinded parent study, the subject dose and schedule on the current study remained the same as the final dose on the parent study, provided that the subject received clinical benefit at that dose. If the subject didn't have a documented clinical benefit on the parent study, the subject began at 750 µg weekly. Regardless of the subject's starting dose on this study, dose adjustments were permitted per the dose adjustment rules.

Romiplostim was initially administered by the investigator or qualified designee during in-clinic visits. At the investigator's discretion, after the first cycle of treatment, subjects who achieved an International Working Group (IWG)-defined platelet response without romiplostim dose adjustments for 4 consecutive weeks were eligible to self-administer romiplostim or have the injection administered by a caregiver outside of the investigational clinic site.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Not applicable.

Duration of Treatment: Subjects received romiplostim as part of Study 20060197 for up to 3.5 years not including treatment during parent studies. All subjects were required to complete an end-of-study (EOS) visit 4 weeks after the last dose of romiplostim. Subsequent to the EOS visit, all subjects continued in the long-term survival follow-up. Each subject was contacted by the site every 24 weeks (± 2 weeks) after his/her EOS visit to assess disease status until the end of the study.

Study Endpoints:

Safety Endpoint:

The primary endpoint was the incidence of all adverse events including clinically significant changes in laboratory values and incidence of antibody formation.

Efficacy endpoints:

The secondary endpoints for this study are as follows:

- The incidence of bleeding events
- The incidence of platelet transfusions
- For subjects with disease-related thrombocytopenia at study entry: The duration of platelet response.

Statistical Methods: The statistical analysis planned for this open-label extension study was descriptive in nature. No formal comparison was performed. Descriptive statistics for demographic and baseline characteristics were summarized for all enrolled subjects. For categorical variables, the number and percentage of subjects in each category were summarized. Continuous variables were summarized by n, mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75th percentile), minimum, and maximum values. For time-to-event variables, the Kaplan-Meier method was used to estimate the quartiles of the variable for the cohort, along with 95% two-sided confidence interval. Time-to-event data were also summarized graphically by plotting Kaplan- Meier estimates. Data were also summarized by the parent studies from which subjects were enrolled since each parent study differed in the use (yes/no) and type (azacitidine, decitabine, lenalidomide) of MDS disease-modifying therapy. This represents a change from the planned analysis.

Summary of Results:

Subject Disposition: All subjects (100%) entering the study received romiplostim at an appropriate dose according to the dose adjustment rules described in the study protocol. Treatment with investigational product was discontinued for subjects from all parent studies prior to study completion due to the recommendation by the Study 20060198 data monitoring committee (DMC); 54 subjects (75%) entered the long-term follow-up (LTFU) phase.

Baseline Demographics:

Sex: Female: 32 (44.4%), Male: 40 (55.6%)

Age: mean (standard deviation [SD]) = 68.9 (11.1) years

Ethnicity/Race: White or Caucasian: 61 (84.7%)
African American: 4 (5.6%)
Hispanic or Latino: 3 (4.2%)
Other: 4 (5.6%)

Efficacy Results: The majority of subjects showed a platelet response within the first 8 weeks of treatment regardless of which parent study the subjects had originally enrolled. Sixty one subjects (84.7%) demonstrated a platelet response by International Working Group criteria during the treatment period with median time to first platelet response at 2.1 weeks and a median duration of 34.6 weeks per subject year. The annualized weekly bleeding event rate was 1120.5 per 100 subject-years and the annualized platelet transfusion event rate was 204.4 per 100 subject-years. The exposure-adjusted incidence of bleeding events generally declined over time. Similarly, the exposure-adjusted transfusion incidence rate declined over time up to 60 weeks of treatment.

Safety Results: No new safety concerns were identified in Study 20060197. Four (5.6%) subjects reported treatment-related serious adverse events (chronic myeloid leukemia, pulmonary fibrosis, hemorrhage intracranial and cerebral ischemia, and speech disorder). Four (5.6%) subjects experienced fatal adverse events, one each for the following preferred terms: pulmonary fibrosis, muscular dystrophy, cardiac arrest, and congestive cardiac failure. No neutralizing antibodies to romiplostim were observed.

The majority of treatment discontinuations (37 subjects) occurred as a result of the Study 2006198 data monitoring committee (DMC) recommendation.

Clinically significant adverse events (ie, events of interest) investigated during the study included thrombotic/thromboembolic events, hematopoietic erythropenia and leukocytosis events, hematopoietic malignancies, hemorrhages, immunogenicity events, non-hematologic malignancies, renal impairment events, bone marrow reticulin firbrosis, bone marrow collagen fibrosis, thrombocytosis events, cardiac disorders, hepatic disorders, MDS disease progression, and MDS disease progression to AML or death.

The following events of interest were not experienced by any subject in Study 20060197: immunogenicity events, bone marrow reticulin fibrosis, thrombocytosis, and bone marrow collagen fibrosis.

Four subjects (5.6%) reported thromboembolic events. Events included one case of each of the following: cerebral ischemia, myocardial infarction, thrombophlebitis, and thrombosis.

Five subjects (6.9%) experienced hematopoietic erythropenia and leukocytosis occurring within a 4-week window.

Three subjects (4.2%) experienced hematopoietic malignancies in Study 20060197, which included the following preferred terms: B-cell lymphoma, chronic myeloid leukemia, diffuse large B-cell lymphoma, and lymphoma. One subject presented with B-cell lymphoma, which was reported under two preferred terms (B-cell lymphoma and lymphoma).

Forty-nine subjects (68.1%) reported hemorrhages.

Three subjects (4.2%) reported non-hematologic malignancies, which included the following preferred terms: neoplasm skin, prostate cancer, and squamous cell carcinoma.

Three subjects (4.2%) reported renal impairment adverse events, which included the following preferred terms: renal failure acute and renal failure. All 3 subjects had risk factors for renal impairment.

Six subjects (8.3%) reported cardiac disorders. These events included the following preferred terms: angina pectoris, arrhythmia, congestive cardiac failure, coronary artery disease, and myocardial infarction. All 6 subjects had prior risk factors for cardiac disorders.

Four subjects (5.6%) reported hepatic disorders. These events included the following preferred terms: ascites, hepatic cirrhosis, hepatic encephalopathy, hepatic pain, liver function test abnormal, prothrombin time prolonged, and varices esophageal. One subject had a risk factor for hepatic disorder.

Twenty-three subjects (31.9%) completed the EOS bone marrow assessment necessary to evaluate disease progression. MDS disease progression, as defined above, was observed in 4 of these 23 evaluable subjects.

Five subjects (6.9%) experienced MDS disease progression to AML on treatment or in long-term follow-up (LTFU) in Study 20060197. Only one subject ([redacted]) was reported to have an increase in peripheral blast cell counts to > 20% at end of study; this subject did not have disease progression to AML.

Safety Discussion: Although Study 20060197 was a single-arm study, the composite rate of MDS disease progression to AML or death was within the expected rate for a population of MDS patients with thrombocytopenia, with an annualized event rate for death or AML of 13.9% (95% CI: 7.9%, 22.5%). The rate of disease progression to AML or death for a similar MDS population (low or intermediate-1 risk) with thrombocytopenia was 20.5% based on an analysis of the International Myelodysplastic Syndromes Risk Analysis Workshop database.

Conclusions: Romiplostim was effective in increasing platelet levels in low or intermediate-1 risk MDS patients with thrombocytopenia. The overall observed safety and efficacy profiles were similar to those seen in other romiplostim studies with MDS subjects. Romiplostim treatment, consistent with previous MDS studies, continued to demonstrate the ability to increase platelet counts in this population.

No subjects had neutralizing antibodies to romiplostim or thrombopoietin (TPO) at any time after receiving romiplostim.

The efficacy of romiplostim therapy in the study population was supported by a decrease in platelet transfusion requirement over time up to 60 weeks of treatment and the overall decrease in significant bleeding events for every 12-week period compared to weeks 1 to 12. Analysis of severe, serious, and fatal events, as well as review of the events of interest, through the treatment period and long-term follow-up, did not reveal any new safety concerns.