2. SYNOPSIS

Name of Sponsor:
Amgen Inc., Thousand Oaks, CA USA

Name of Finished Product:
Romiplostim

Name of Active Ingredient:
Romiplostim (AMG 531)

Title of Study:
An Open Label Study of Romiplostim in Adult Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP)

Investigator(s) and Study Center(s):
This is an international, multicenter study. One hundred and six centers in the United States, Canada, the EU, and Australia enrolled subjects in this study. Centers and principal investigators are listed in Appendix 4.

Publication(s):
Janssens A, Tarantino MD, Bird R, et al. Final Results From an international, Multi-center, Single-arm Study Evaluating the Safety and Efficacy of Romiplostim in Adults with Primary Immune Thrombocytopenia. *Blood.* 2011;118: Abstract 3279.

Janssens A, Tarantino M, Bird R, et al. Interim Results From An International, Multi-center, Single-arm Study Evaluating the Safety and Efficacy of Romiplostim in Adults With Primary Immune Thrombocytopenia (ITP). *Haematologica.* 2011;96:Abstract 0223.

Study Period:
The first subject was enrolled on 24 February 2005 and the last subject visit was on 07 January 2011.

Development Phase: 3b

Objectives:
This study was designed to provide romiplostim to adult thrombocytopenic subjects with ITP who had received at least one prior therapy for their disease. This protocol expanded the understanding of the safety of romiplostim in adult ITP subjects with thrombocytopenia. The primary objective of the study was to evaluate the safety of romiplostim in adult thrombocytopenic subjects with ITP and the secondary objective was to evaluate hematological responses to romiplostim.

Methodology:
This study provided open-label romiplostim to adult thrombocytopenic subjects with ITP who had received at least one prior therapy for ITP.

The protocol was designed to expand the understanding of the safety profile of romiplostim in adult ITP subjects with thrombocytopenia.

Romiplostim was administered by subcutaneous (SC) injection once per week. Subjects entered the study with a starting dose of 1 µg/kg, dose adjustments were allowed throughout the study and were based on platelet counts. Weekly dose increases in increments of 1 µg/kg were allowed in order to achieve and maintain a target platelet count of ≥ 50 x 10^9/L. Each subject's maintenance romiplostim dose was identified once the target platelet count was maintained for 4 weeks without dose adjustments. Additional dose adjustments were made according to prespecified dose adjustment rules.

Subjects who achieved a stable dose of romiplostim for at least 4 weeks were allowed to self-administer romiplostim.

A subject with a platelet count of ≤ 20 x 10^9/L after receiving 10 µg/kg romiplostim for 4 consecutive weeks was considered to be a non-responder and was discontinued from the study; investigators could be granted an exception to this rule by Amgen per Amgen and PI clinical judgment.

If, in the opinion of the investigator, the subject maintained an acceptable platelet count without weekly dosing of romiplostim, administration was held until the platelet count fell to < 50 x 10^9/L, or the subject completed the study. Once the platelet count fell to < 50 x 10^9/L, dosing of romiplostim resumed at the same dose as previously given to the subject. The maximum permitted dose of romiplostim was 10 µg/kg.

Rescue therapies were allowed at any time during the study. Reductions in concurrent ITP therapies were allowed at any time when platelet counts were > 50 x 10^9/L.

Number of Subjects Planned:
The number of subjects in this study was governed by the number of ITP subjects who met all inclusion and exclusion criteria; it was estimated that approximately 500 subjects were to enroll into the study.

Number of Subjects Enrolled: A total of 407 subjects enrolled in the study.

Diagnosis and Main Criteria for Eligibility:
Eligible adult subjects were those who had been diagnosed with immune (idiopathic) thrombocytopenic purpura per the American Society of Hematology guidelines (George et al, 1996) who had received at least 1 prior therapy for ITP and who had a platelet count of ≤ 30 x 10^9/L and/or who had experienced bleeding that was uncontrolled with conventional therapies.

Key criteria that excluded subjects from participation were a history of hematological malignancy, myeloproliferative disorders, myelodysplastic syndromes (MDS), or bone marrow disorders, a current pregnancy or breast feeding, a known hypersensitivity to any recombinant *E coli*-derived product, participation in any study evaluating polyethylene glycol-conjugated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF), recombinant human thrombopoietin (rHuTPO), or a related platelet product, or had received any therapeutic drug or device that was not approved by the local regulatory health agency for any indication within 4 weeks of screening.

A complete list of inclusion/exclusion criteria can be found in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:
Romiplostim was supplied in a 5-mL single-use vial as a sterile, white, preservative-free, lyophilized powder. After reconstitution with sterile water for injection, romiplostim is available at a concentration of 0.5 mg/mL. Romiplostim was administered SC once weekly at a starting dose of 1 µg/kg. The manufacturing lot numbers for romiplostim used in this study were [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:
None

Duration of Treatment:
Romiplostim was administered by subcutaneous (SC) injection once weekly until discontinuation or withdrawal from the study. If a subject discontinued romiplostim for any reason, the subject was to complete the end-of-treatment visit assessments 2 weeks after the last dose of romiplostim and the end-of-study visit assessments 4 weeks after the last dose of romiplostim.

Study Endpoints:

The following endpoints were identified in the Statistical Analysis Plan (SAP), Version 3.0, dated 16 June 2010, and the clinical protocol, Amendment 4, Superceding Version, dated 14 August 2008.

Primary / Safety Endpoint:

Incidence of adverse events, including clinically significant changes in laboratory values, and incidence of antibody formation

Secondary / Efficacy Endpoint:

Incidence of platelet response evaluated using the following definitions:

- a doubling of baseline platelet count and a platelet count of $\geq 50 \times 10^9$/L
- a platelet count increase of $\geq 20 \times 10^9$/L from baseline

Statistical Methods:

One hundred sixty-eight subjects enrolled under the original protocol and Protocol Amendments 1 through 3. Two hundred thirty-nine subjects enrolled under Protocol Amendment 4. The safety and efficacy endpoints were summarized in this report according to the analyses described in the SAP (Appendix 2), Version 3.0, dated 16 June 2010.

The analyses of safety and efficacy were conducted using all enrolled subjects who received at least 1 dose of romiplostim**.**

Descriptive statistics were used to summarize demographics, subject disposition, extent of exposure, adverse events, laboratories, vital signs, antibody, and platelet response results. Continuous data were summarized using the following summary statistics: n, mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), and minimum and maximum. Categorical assessments were summarized by the number and percentage of subjects in each category. Graphical summaries of assessments over time and individual subject listings were presented.

Summary of Results:

Subject Disposition:

A total of 407 subjects enrolled at 106 study centers and received at least one dose of romiplostim. Two hundred eighty-eight (71%) subjects completed the study and 119 (29%) subjects discontinued from the study. Subjects were considered to have completed the study if a subject no longer required treatment with romiplostim due to resolved ITP, a subject transitioned into Amgen Study 20030213, or the study was closed by the sponsor. A majority of subjects (237 out of 407) had been on study > 36 weeks and 41 subjects remained on study by 84 weeks. One subject remained on study for at least 204 weeks.

Baseline Demographics:

Sex: 40% male, 60% female

Median Age: 56 years (range: 18 to [redacted] years)

Ethnicity (Race): White or Caucasian (94%), Hispanic or Latino (2%), Asian (2%), Black or African American (1%), Native Hawaiian or other Pacific Islander (< 1%), other (< 1%)

Efficacy Results:

Three hundred seventy (91%) subjects (95% CI: 88%, 94%) had a doubling of baseline platelet count and a platelet count $\geq 50 \times 10^9$/L. Three hundred eighty (93%) subjects (95% CI: 90%, 96%) had a platelet count increase of $\geq 20 \times 10^9$/L from baseline. By Week 2, 42% of subjects achieved a doubling of the baseline platelet count and a platelet count $\geq 50 \times 10^9$/L, and 52% of subjects achieved a platelet count increase of $\geq 20 \times 10^9$/L. Though

response to treatment was rapid, the starting dose for 168 out of 407 subjects was 3 µg/kg (those subjects enrolled under the original protocol or protocol amendments 1 through 3), compared to the 1 µg/kg starting dose for subjects enrolled under protocol amendment 4. At baseline, platelet counts ranged from 0 x 10^9/L to 170 x 10^9/L with a median of 14.0 x 10^9/L (Q1, 8.0; Q3, 21.0); there were 5 subjects ([redacted], [redacted], [redacted], [redacted], and [redacted]) with protocol deviations in which subjects were incorrectly enrolled with a platelet count higher than that allowed in the protocol. The median peak platelet count for all subjects on study drug was 346.00 x 10^9/L (Q1, 180.00; Q3, 563.00).

Safety Results:

Three hundred seventy-seven (92.6%) subjects reported at least one adverse event. The duration of treatment varied greatly among subjects. The median duration of treatment for the 407 subjects in the safety analysis set was 44.29 weeks (Q1, 20.43; Q3, 65.86) with a range of 1.9 to 201.0 weeks. Subjects in the safety analysis set had a total of 20,201 subject-weeks on study and reported a total of 4541 adverse events (22.5 events per 100 subject-weeks on study). The adverse events with the highest study duration-adjusted event rates (events per 100 subject-weeks on study) were similar to those with highest subject incidence: headache (0.9), contusion (0.8), petechiae (0.6), epistaxis (0.6), nausea (0.5), arthralgia (0.5), fatigue (0.5), thrombocytopenia (0.5), and nasopharyngitis (0.5).

Treatment-emergent adverse events were reported as treatment related for 193 (47.4%) subjects. Treatment-related adverse events with highest study duration-adjusted event rates (events per 100 subject-weeks on study) were headache (0.4), fatigue (0.2), and arthralgia (0.2).

Serious adverse events were reported for 122 (30.0%) subjects, resulting in a study duration-adjusted rate of 1.6 per 100 subject weeks. Serious adverse events with highest study duration-adjusted event rates (events per 100 subject-weeks on study) were thrombocytopenia (0.2) and epistaxis (0.1). The study-duration adjusted event rates all other serious adverse events had duration-adjusted event rates were < 0.1 events per 100 subject-weeks.

Twenty-nine (7.1%) subjects had serious adverse events that were considered treatment related. The duration-adjusted event rate for all treatment-related serious adverse events was 0.2 per 100 subject-weeks. Treatment-related serious adverse events were < 0.1 events per 100 subject-weeks for each preferred term. The most commonly reported (each experienced by 2 [0.5%] subjects) treatment-related serious adverse events were bone marrow reticulin fibrosis (see Section 11.6 for more information), cerebrovascular accident, deep vein thrombosis, hemorrhage, headache, nausea, and pulmonary embolism. All other treatment-related serious adverse events were experienced by 1 (0.2%) subject.

Treatment-emergent adverse events leading to study discontinuation were reported for 29 subjects (7.1%). The study-duration adjusted event rate for all adverse events leading to study discontinuation was 0.1 event per 100 subject-weeks. Adverse events leading to study discontinuation were < 0.1 events per 100 subject-weeks for each preferred term. The most commonly reported (each experienced by 2 [0.5%] subjects) treatment-emergent adverse events leading to study discontinuation were pulmonary embolism and renal failure. All other treatment-emergent adverse events leading to study discontinuation were each reported in 1 (0.2%) subject. Sixteen of these 29 subjects discontinued from the study because of a treatment-emergent adverse event that was considered treatment-related.

Eighteen (4.4%) subjects died (0.1 events per 100 subject-weeks) as a result of the following events: renal failure, acute respiratory distress syndrome, aplastic anemia, brain edema, cardiac failure, cytomegalovirus infection, fungal sepsis, hemolysis, intracranial hemorrhage, intestinal infarction, intestinal ischemia, intracranial venous sinus thrombosis, ischemic stroke, osteomyelitis, decreased platelet count, pneumonia, and sudden death. Two (0.5%) subjects died as a result of renal failure and 1 (0.2%) subject died from each of the other events. Only the hemolysis, aplastic anemia, and intestinal ischemia that resulted in death were considered treatment-related; all other deaths were not considered treatment-related. The subject that died from hemolysis was diagnosed with a urinary tract infection and subsequently failed antibiotic therapy. The subject was then hospitalized and experienced disseminated intravascular

coagulation. The subject that died from aplastic anemia also had macrocytic anemia at baseline. The subject that died from intestinal ischemia had hepatopathy (hepatitis B and C) at baseline and developed portal vein thrombosis prior to experiencing intestinal ischemia.

Clinically significant adverse events (ie, events of interest) investigated during the study included thrombotic/thromboembolic, thrombocytosis, hematopoietic malignancies/MDS, non-hematologic malignancies, hemorrhage, immunogenicity, leukocytosis and anemia, renal impairment, and bone marrow reticulin and bone marrow collagen fibrosis events.

Twenty-six (6.4%) subjects experienced a thrombotic or thromboembolic event (36 events) during the study. The study duration-adjusted incidence of a thrombotic/thromboembolic event was 0.2 events per 100 subject-weeks.

Twelve (2.9%) subjects experienced at least 1 of the 17 thrombocytosis events during the study (0.1 events per 100 subject-weeks).

One (0.2%) subject experienced a hematopoietic malignancy/MDS event. Though not a hematologic malignancy, the event (aplastic anemia) met the search criteria for a hematopoietic malignancy/MDS event of interest. This subject also presented with macrocytic anemia at baseline.

Five (1.2%) subjects experienced a non-hematologic malignancy event (5 events) during the study. None of the events were considered related to study drug and none were fatal.

One hundred ninety-seven (48.4%) subjects experienced at least one hemorrhage event during the study (4.1 events per 100 subject-weeks).

Forty-five (11%) subjects reported at least 1 event during the study of leukocytosis and anemia.

Four (1.0%) subjects experienced a renal impairment event during the study. All renal failure events were considered serious and none was considered related to study drug.

Four (1.0%) subjects each experienced one bone marrow fibrosis/reticulin event during the study. The preferred term bone marrow disorders accounted for 2 events and the preferred term bone marrow reticulin fibrosis accounted for 2 events. All 4 events were consistent with bone marrow reticulin and were considered related to study drug. Both of the bone marrow reticulin events and 1 of the bone marrow disorder events were considered serious. One (0.2%) subject experienced a bone marrow collagen fibrosis event (preferred term bone marrow disorder) during the study that was not considered related to study drug. The subject had positive trichrome staining, consistent with type I collagen; [redacted]. The presence of type I collagen is primarily associated with myeloproliferative diseases and metastatic solid tumors (Kuter et al, 2007).

There was 1 (0.2%) subject that experienced an event that met the search criteria for an immunogenicity event of interest (no therapeutic response). The event was considered serious, severe, and not related to study drug. The subject did not develop neutralizing antibodies to romiplostim or endogenous thrombopoietin (eTPO).

Twenty (5%) of the 394 subjects that were assessed for antibodies were positive for binding antibodies to romiplostim/romiplostim peptide and 19 of 394 subjects (5%) were positive for binding antibodies to TPO postdosing with romiplostim.

Thirteen of 394 subjects (3%) had pre-existing antibodies to romiplostim and 8 of the 394 subjects (2%) had pre-existing antibodies to TPO.

One subject (0.3% of the subjects that were assessed for antibodies) was positive for neutralizing antibodies to romiplostim at screening but no neutralizing antibodies to romiplostim were noted at the last time point. Despite being positive for neutralizing antibodies at screening, the subject had a platelet response by week 2, which was maintained throughout treatment. All other subjects were negative for neutralizing antibodies to eTPO.

Subjects achieving a stable dose of romiplostim for at least 4 consecutive weeks were allowed to self-administer romiplostim. The 215 subjects who self-administered treatment were on treatment for a mean of 15.99 (SD, 16.54) weeks prior to self-administration and those subjects

self-administered treatment for a mean of 38.0 (SD, 25.9) weeks. Of the 215 subjects who started self-administration, 52 discontinued self-administration. Reasons for discontinuation of self-administration included administrative decision (41 subjects), subject request (9 subjects), and noncompliance (2 subjects). During the 3 weeks prior to initiation of self-administration, the mean percent of time that subjects had a platelet response (ie, doubling of the baseline platelet count and a platelet count ≥ 50 x 10^9/L) was 84.1% (SD, 30.1), compared to 78.7% (SD, 28.7) from the time of initiation of self-administration to the end-of-treatment (EOT). During the 3 weeks prior to initiation of self-administration, the mean percent time (weeks) that subjects had a platelet response (ie, platelet count increase of ≥ 20 x 10^9/L from baseline) was 90.5% (SD, 21.9), compared to 86.1% (SD, 23.0) from the time of initiation of self-administration to the EOT. Although the platelet responses were slightly lower during the self-administration period, the difference could not be assessed statistically because of the much shorter time period prior to self-administration (3 weeks) than the period of self-administration (mean duration of 38 weeks).

Self-administration of romiplostim was well-tolerated. For the population that self-administered, the duration-adjusted adverse event rate was lower during the self-administration period (12.6 events per 100 subject-weeks) than that for the 3 weeks prior to self-administration (22.3 events per 100 subject-weeks). Likewise, the duration-adjusted treatment-related adverse event rate was lower during the self-administration period (1.6 events per 100 subject-weeks) than that for the 3 weeks prior to self-administration (5.3 events per 100 subject-weeks). The duration-adjusted serious adverse event rates were 0.3 events per 100 subject-weeks during the 3 weeks prior to self-administration and 0.9 events per 100 subject-weeks for the self-administration period. There were no treatment-related serious adverse events reported during the 3-week time period prior to self administration and only 0.2 treatment-related serious adverse events per 100 subject-weeks during the self-administration period. The rate of duration-adjusted adverse events and duration-adjusted treatment-related adverse events leading to discontinuation of investigational product or discontinuation of the study were similar across the 2 treatment periods for subjects who self-administered.

Conclusions:

This was a phase 3b study in which romiplostim was administered to subjects with ITP who did not respond to at least 1 other treatment. Romiplostim was well-tolerated by these subjects and was able to induce platelet responses within weeks of starting treatment in the majority of subjects enrolled. This study allowed for an extended treatment duration of romiplostim during which there were no newly recognized safety concerns nor a reduction of efficacy (hematological responses) over time. This study also demonstrated that subjects could safely and effectively self-administer romiplostim treatment. [redacted]