2. SYNOPSIS

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

Name of Finished Product: Nplate®

Name of Active Ingredient: Romiplostim

Title of Study: A Randomized, Controlled, Open-label Study Evaluating the Efficacy and Tolerability of AMG 531 versus Medical Standard of Care as Chronic Therapy for Non-splenectomized Subjects with Immune (Idiopathic) Thrombocytopenic Purpura

Investigator(s) and Study Center(s): This was a multi-center, multi-national study conducted at 85 centers in the United States, Canada, the European Union, and Australia. Centers and principal investigators are listed in Appendix 4.

Publication(s):
Rummel M, Boccia R, Macik G, et al. Efficacy and safety of romiplostim versus medical standard of care as chronic therapy for nonsplenectomized patients with immune thrombocytopenia (ITP). Presented at: 14th Congress of the European Hematology Association; June 4-7, 2009; Berlin, Germany. Abstract 1059.

Kuter DJ, Rummel MJ, Boccia RV, et al. Comparison of splenectomy and treatment failure incidence in nonsplenectomized patients with immune thrombocytopenia (ITP) receiving romiplostim or medical standard of care: 1-year treatment and 6-month safety follow-up. Presented at: 51st American Society of Hematology Annual Meeting and Exhibition; December 5-8 2009; New Orleans, Louisiana. Abstract 679.

Study Period: 19 December 2006 to 11 May 2009

Development Phase: 3b

Introduction and Objectives:

Immune (idiopathic) thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by persistent thrombocytopenia due to antibody binding to platelet antigen(s) causing their premature destruction by the reticuloendothelial system, particularly the spleen (Provan et al, 2003). The thrombocytopenia places patients at risks for bruising or mucocutaneous bleeding.

While there are practice guidelines in the US and Europe for the treatment of ITP (George et al, 1996; Provan et al, 2003), there is little to no data from controlled studies available to support the use of 1 therapy over another. Available therapies such as glucocorticoids have variable response rates and result in substantial side effects, limiting their use for long-term treatment (Cines and McMillan, 2005; Cines and Bussel, 2005).

Romiplostim (AMG 531) is a recombinant protein that is expressed in *E coli* and has been shown to increase platelet counts in healthy human subjects and in subjects with ITP. Romiplostim stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO), but no sequence homology exists between romiplostim and eTPO, thereby reducing the probability of antibodies to romiplostim binding to eTPO and causing thrombocytopenia.

The primary objective of this study was to compare the ability of romiplostim versus medical standard of care (SOC) to prevent a splenectomy and to provide a durable treatment option for ITP non-splenectomized adult subjects during the 52-week treatment period.

The secondary objectives of the study were to observe the impact of romiplostim on various ITP symptoms and platelet parameters compared to medical SOC for ITP. These include the time to splenectomy, platelet response, and the change in ITP Patient Assessment Questionnaire (PAQ) Physical Health domains of Symptoms, Bother, Activity, and Fatigue.

Methodology:

This was a phase 3b, multi-center, randomized, SOC-controlled, open-label, 52-week treatment study to compare romiplostim to medical SOC for ITP in non-splenectomized subjects who were 18 years or older and who had received at least 1 prior therapy for ITP. The study included a 6-month safety follow-up. Eligible subjects were randomized in a 2:1 ratio to romiplostim or medical SOC for ITP if their platelet count was $< 50 \times 10^9$/L or their platelet count fell to $< 50 \times 10^9$/L during or after a clinically-indicated taper or discontinuation of current ITP therapy. Randomization was stratified by geographic region. Subjects randomized to romiplostim must have completed the taper or discontinuation of medical SOC for ITP as soon as medically feasible after the initiation of romiplostim.

Romiplostim was administered by subcutaneous (SC) injection once weekly starting at a dose of 3 μg/kg, adjusted as needed throughout the study to a maximum dose of 10 μg/kg in order to maintain platelet counts between 50 and 200 $\times 10^9$/L. Following week 8, subjects who achieved a stable dose of romiplostim for at least 3 weeks were allowed to self-inject romiplostim, at the investigator's discretion. Medical SOC treatments were selected and prescribed by the investigator according to standard institutional practices or therapeutic guidelines. Dose adjustment of medical SOC for ITP was allowed throughout the study. After the completion or discontinuation of the study treatment period, any subject who did not transfer into another romiplostim study was to complete a 6-month safety follow-up period.

Adverse events and concomitant medications were assessed continually throughout the study.

Number of Subjects Planned: The total number of subjects planned for the study was 210 (140 randomized to romiplostim, 70 randomized to SOC).

Number of Subjects Enrolled: 234 (157 romiplostim, 77 SOC)

Sex: 131 (56%) women, 103 (44%) men

Age: Median 57 years (range: 18 to 90 years)

Ethnicity (Race): 88% white/Caucasian, 6% Hispanic/Latino, 3% black/African American, 3% Asian, < 1% American Indian/Alaska Native

Diagnosis and Main Criteria for Eligibility: Eligible subjects were non-splenectomized adults ≥ 18 years of age who had a diagnosis of ITP according to the American Society of Hematology (ASH) guidelines (George et al 1996), had received at least 1 prior therapy for ITP, and had a platelet count $< 50 \times 10^9$/L or their platelet count fell to $< 50 \times 10^9$/L during or after a clinically-indicated taper or discontinuation of current ITP therapy. Criteria for exclusion from the study included, but were not limited to, an active malignancy; a history of cancer other than basal cell carcinoma or cervical carcinoma in situ, with treatment or active disease within 5 years; a known history of bone marrow stem cell disorder; previous participation in any study evaluating pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF), recombinant human thrombopoietin (rHuTPO), romiplostim, or a thrombopoietic protein; pregnancy or breast feeding; or a known sensitivity to any recombinant *E coli*-derived product.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Romiplostim was presented as a sterile, white, preservative-free, lyophilized powder in 5.0 mL single-use glass vials containing a protein concentration equivalent to 0.5 mg/mL [redacted]. Romiplostim was administered weekly by SC injection at a starting dose of 3 µg/kg. At the investigator's discretion, subjects who achieved a stable dose of romiplostim for at least 3 consecutive weeks were allowed to self-inject romiplostim. Dose adjustments were made according to specified guidelines. The maximum permitted dose of romiplostim was 10 µg/kg. Romiplostim fill lot numbers [redacted], [redacted], [redacted], [redacted], and [redacted] were used in this study.

Duration of Treatment: The maximum duration of treatment for each subject was 52 weeks.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Medical SOC treatments were administered to subjects randomized to the SOC arm. Medical SOC treatments were selected and prescribed by the investigator and administered according to standard institutional practices or therapeutic guidelines. Medical SOC treatments were obtained through the usual commercial routes.

Study Endpoints

Primary Efficacy Endpoints: This study had two primary endpoints, one related to splenectomy and the other related to treatment failure. The first primary endpoint was the number of subjects undergoing a splenectomy during the 52-week treatment period by randomized treatment group. The second primary endpoint was the number of subjects with a treatment failure during the 52-week treatment period by randomized treatment group. Treatment failure was defined as:

- a lack of efficacy, defined as a platelet count ≤ 20 x 10^9/L for 4 consecutive weeks at the highest recommended dose and schedule (romiplostim - 10 µg/kg weekly; medical SOC for ITP - apply standard institutional practices or therapeutic guidelines); or,
- a major bleeding event; or,
- a change in therapy due to an intolerable side effect or bleeding symptoms (including a minor bleeding event)

Secondary Efficacy Endpoints: The secondary endpoints included the following:

- time to splenectomy, calculated in days from the date of randomization to the date of splenectomy during the 52-week treatment period,
- number of platelet responses, defined as platelet counts > 50 x 10^9/L at each scheduled visit,
- change in the ITP Patient Assessment Questionnaire (ITP-PAQ) Physical Health domains of Symptoms, Bother, Activity, and Fatigue

Safety Endpoint: The safety endpoints were adverse events, major and minor bleeding events, and an evaluation of abnormal laboratory values.

Statistical Methods:

The Cochran-Mantel-Haenszel chi-squared test was used to compare the number of subjects undergoing splenectomy and the number of subjects experiencing treatment failures during the 52-week treatment period (the primary endpoints) between the romiplostim and medical SOC treatment groups, controlling for the geographic location of the investigational sites. Subjects who discontinued study during the 52-week treatment period prior to reporting an event were considered to have had an event. The common odds ratio and its 95% confidence interval (CI) were estimated. The proportion of subjects undergoing splenectomy and the proportion of subjects experiencing treatment failure were provided by treatment group with 95% CIs. Sensitivity analyses were performed, comparing the incidence of subjects who actually reported a splenectomy procedure and the incidence of subjects who actually met the treatment failure definition between the two treatment groups.

As a secondary analysis for the primary endpoints, the multiple logistic regression model for each primary efficacy endpoint was employed to adjust for baseline covariates for any imbalance between treatment groups found such as age, gender, race, and subject baseline characteristics (concurrent ITP therapy). In another analysis of the primary endpoint, the rates of splenectomy and treatment failure by the end of the 52-week treatment period were also estimated for the treatment groups using Kaplan-Meier methods. Time to splenectomy was also compared between the treatment groups using the Kaplan-Meier method and stratified log-rank test.

Platelet response was counted for each subject up to the time of splenectomy or the end-of-treatment visit, whichever came first. The number of platelet responses was summarized as exposure-adjusted incidence rate by treatment group. [redacted].

The following sequential testing scheme was employed to adjust for multiplicity of the primary and secondary endpoints in comparing romiplostim versus medical SOC for ITP based on the order of clinical importance. All tests were compared at a significance level of 0.05 (2-sided).

- test the number of subjects undergoing a splenectomy and the number of subjects with a treatment failure; if both are significant in favor of romiplostim over medical SOC for ITP,
- test the time to splenectomy; if significant in favor of romiplostim over medical SOC for ITP, and
- test the number of platelet responses.

Change from baseline in the patient-reported outcome (PRO) endpoint was summarized by treatment group at each time point of PRO measurement. A mixed-effects linear model was used to test a significant difference in improvement from baseline (week 1) to the end-of-treatment visit. Inferences for PRO endpoints were made only after the test of primary efficacy endpoints were statistically significant in favor of romiplostim over medical SOC for ITP. Holm's testing method was performed to adjust for multiplicity.

Summary of Results:

Subject Disposition: A total of 234 subjects were randomized at 85 study centers throughout the European Union, North America, and Australia. One hundred fifty-seven subjects were randomized to the romiplostim treatment group and 77 subjects were randomized to the medical SOC treatment group. Of the 234 subjects in the study, 3 (1.9%) subjects randomized to the romiplostim group and 2 (2.6%) subjects randomized to the SOC group did not receive treatment on study. Overall, 181 subjects (130 [82.8%] randomized to romiplostim and 51 [66.2%] randomized to SOC) completed the study. Fifty-three (22.6%) subjects overall, 27 (17.2%) in the romiplostim group and 26 (33.8%) in the SOC group, discontinued the study early. A total of 6 subjects (1 in the romiplostim group and 5 in the SOC group) died during the study.

Efficacy Results: In both primary endpoint analyses, the efficacy of romiplostim was found to be significantly greater (ie, lower rates of splenectomy and treatment failure) than that of medical SOC. The overall subject incidence of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group. The p-value for the treatment difference between groups is < 0.0001, with an odds ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35), indicating that the odds of undergoing a splenectomy is statistically significantly lower in the romiplostim group than the SOC group.

For the co-primary endpoint, the overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group. The p-value for the treatment difference between groups is 0.0005, with an odds ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61), indicating that the odds of experiencing treatment failure is statistically significantly lower in the romiplostim group than the SOC group.

The primary analyses considered subjects who discontinued the study to have a splenectomy event and treatment failure. Therefore, a sensitivity analysis was performed comparing only subjects who actually reported a splenectomy procedure in the romiplostim (2 [1.3%] subjects) and SOC (15 [19.5%] subjects) groups. The p-value for this treatment difference is < 0.0001, with an odds ratio (romiplostim vs SOC) of 0.05 (95% CI: 0.01, 0.24). Similarly, a sensitivity analysis of treatment failures in the romiplostim (6 [3.8%] subjects) and SOC (10 [13.0%] subjects) groups was performed. The p-value for this treatment difference is 0.0089, with an odds ratio (romiplostim vs SOC) of 0.26 (95% CI: 0.09, 0.75).

Kaplan-Meier estimates of time to splenectomy also showed a difference in favor of romiplostim over SOC (p < 0.0001). This result was confirmed by Cox-regression analysis which yielded a hazard ratio (romiplostim vs SOC) of 0.05 (95% CI: 0.01, 0.24; p = 0.0001), indicating that subjects in the romiplostim group were 95% less likely to undergo a splenectomy during the treatment period compared with those in the SOC group.

Platelet responses were also consistently achieved by a higher proportion of subjects in the romiplostim group compared with those in the SOC group starting from week 2. Poisson regression analyses indicated that romiplostim subjects were 2.3 times more likely to have a platelet response than subjects in the SOC group (p < 0.0001).

None of the baseline covariates of age, gender, race, and baseline ITP characteristics (time since ITP diagnosis) were found to be a significant predictor of the incidence of splenectomy. However, time since ITP diagnosis was found to be a significant factor in the incidence of treatment failure and time to splenectomy, with subjects with ≤ 3 years since ITP diagnosis less likely to have treatment failure and more likely to undergo splenectomy at the next time point compared to subjects with > 3 years since ITP diagnosis. In addition, prior ITP treatments was found to be a significant factor in platelet response, with subjects with ≤ 3 prior ITP treatments having a higher chance of platelet response than subjects with > 3 prior ITP treatments. The models for these analyses were adjusted accordingly.

Bleeding events and serious bleeding events were reported in a similar proportion of subjects in the romiplostim and SOC groups. Treatment-related bleeding events occurred in a smaller proportion of subjects in the romiplostim group (6 [3.8%] subjects) than the SOC group (9 [12.3%] subjects). The duration-adjusted incidence rate per 100 subject-weeks (romiplostim, SOC) of the total number of bleeding events (3.56 vs 5.02), grade 2 or higher bleeding events (0.47 vs 0.69), and grade 3 or higher bleeding events (0.11 vs 0.33) was also lower in the romiplostim group compared with the SOC group.

Safety Results: During the overall (52-week) treatment period, adverse events were reported by 149 (95.5%) subjects in the romiplostim group and 67 (91.8%) subjects in the SOC group. The total number of duration-adjusted adverse events (per 100 subject-weeks) was 23.1 in the romiplostim group and 20.9 in the SOC group. The 3 most frequently reported duration-adjusted adverse events (per 100 subject-weeks) in the romiplostim group (romiplostim, SOC) were headache (1.11, 0.85), epistaxis (0.80, 1.18), and fatigue (0.70, 0.62). Eighty-two (52.6%) subjects in the romiplostim group and 29 (39.7%) subjects in the SOC group reported treatment-related adverse events. The total number of duration-adjusted treatment-related adverse events (per 100 subject-weeks) was 3.62 in the romiplostim group and 2.98 in the SOC group. The most common duration-adjusted treatment-related adverse events (per 100 subject-weeks) in both treatment groups (romiplostim, SOC) were headache (0.45, 0.20) and fatigue (0.19, 0.26).

Several adverse events of interest were examined. A higher proportion of subjects in the romiplostim group (8 [5.2%] subjects) than the SOC group (0 subjects) reported both leukocytosis and anemia within a 4-week window during the initial treatment period. Renal impairment was also reported by a higher proportion of subjects in the romiplostim group (21 [13.6%] subjects) than the SOC group (7 [9.3%] subjects) during the initial treatment period. During the initial treatment period, the rates of (romiplostim, SOC) thrombotic or thromboembolic events (6 [3.9%] subjects, 2 [2.7%] subjects), thrombocytosis events (1 [0.6%] subject, 1 [1.4%] subject), hematopoietic malignancies and myelodysplastic syndromes (0 subjects, 2 [2.7%] subjects), and neoplastic events (14 [9.1%] subjects, 5 [6.7%] subjects), were similar between treatment groups. There were no reports of bone marrow fibrosis/reticulin events or immunogenicity events during the initial treatment period.

During the overall treatment period, serious adverse events were reported by 36 (23.1%) subjects in the romiplostim group and 28 (38.4%) subjects in the SOC group. The most common serious adverse event in both treatment groups was thrombocytopenia (6 [3.8%] subjects in the romiplostim group, 8 [11.0%] subjects in the SOC group). Serious treatment-related adverse events during the overall treatment period were reported by 7 (4.5%) subjects in the romiplostim group and 6 (8.2%) subjects in the SOC group. Serious treatment-related adverse events reported in more than one subject in the romiplostim group included pulmonary embolism (3 subjects) and deep vein thrombosis (2 subjects).

A lower proportion of subjects in the romiplostim group than the SOC group reported adverse events (romiplostim, SOC) with CTCAE grade 3 or higher severity (54 [34.6%] subjects, 31 [42.5%] subjects) and CTCAE grade 4 or higher severity (6 [3.8%] subjects, 12 [16.4%] subjects). Similarly, a lower proportion of subjects in the romiplostim group than the SOC group reported treatment-related adverse events (romiplostim, SOC) with CTCAE grade 3 or higher severity (13 [8.3%] subjects, 9 [12.3%] subjects) and CTCAE grade 4 or higher severity (0 subjects, 3 [4.1%] subjects).

The rates of study withdrawal due to adverse events were similar between treatment groups (6 [3.8%] subjects in the romiplostim group, 3 [4.1%] subjects in the SOC group). Adverse events which led to study withdrawal in the romiplostim group included paresthesia, pulmonary embolism, rash, increased splenomegaly, and myocardial infarction; all of these events were considered at least possibly related to treatment by the investigator. Adverse events which led to study withdrawal in the SOC group included rectal cancer, myelodysplastic syndromes, and lymphoma; none of these adverse events was considered related to SOC treatment by the investigator.

Six subjects died during the study, 1 subject in the romiplostim group (pneumonia) and 5 subjects in the SOC group (lung cancer metastatic, left ventricular failure, hepatic failure, hepatic neoplasm malignant, and cardio-respiratory arrest). None of the deaths was considered treatment-related by the investigator.

In summary, the overall safety profile reported for romiplostim was comparable to SOC and consistent with the safety findings from previous studies.

Conclusions: Romiplostim administered weekly by SC injection was well tolerated and significantly reduced the incidences of splenectomy and treatment failure in non-splenectomized subjects with ITP compared with the standard of care.