CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125268

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW
Team Leader's Secondary Review

BLA: 125268/0	Submission Date(s): 10/23, 10/29/07, 1/23, 2/8, 2/22, 3/11, 3/18, 3/21, 3/28, 4/8/08
Brand Name (Generic Name)	Nplate™(Romiplostim)
Sponsor	Amgen
Submission Type; Code	NME, Priority
Relevant IND(s)	BB-IND 10205
PDUFA Date	4/23/08, extended to 7/23/08
Formulation Strength(s)	250 mcg or 500 mcg in single-use vials. Refrigerate lyophilized Romiplostim and protect from light. Do not freeze. Reconstitute with 0.5 mL or 1 mL Sterile Water for Injection, USP (SWI) resulting in 500 mcg/mL for subcutaneous injection (SC)
Proposed Indication	For the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): • Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins. • Who are splenectomized and have an insufficient response to splenectomy.
Proposed Dosing Regimen	• Initial dose of 1 mcg/kg once weekly as a subcutaneous (SC) injection. • Adjust weekly dose by increments of 1 mcg/kg to minimize the risk of bleeding by achieving and maintaining a platelet count greater than or equal to 50 x 10^9/L. Assess the platelet count weekly until a stable platelet count ($\geq$50x10^9/L for at least 4 weeks without dose adjustment) has been achieved and monthly thereafter. • Do not exceed the maximum weekly dose of 10 mcg/kg. • After the platelet count has fallen to <200x10^9/L, resume Nplate at a dose reduced by 1 mcg/kg • Discontinue if platelets count does not increase after 4 weeks at the maximum dose.
Clinical Division	DMIHP
Review Division	Clinical Pharmacology Division 5/OCP
Primary Reviewer	Angela Men, MD, Ph.D.
Secondary Reviewer	Hong Zhao, Ph.D.
Division Director	NAM Atiqur Rahman, Ph.D.

1. Recommendation

The application is acceptable from a Clinical Pharmacology perspective provided that the sponsor and the Agency come to an agreement regarding the language in the package insert and the sponsor commits to the Risk Evaluation and Mitigation Strategy (REMS) Plan and postmarketing studies addressing the safety issues related to the long-term Nplate therapy.

2. Postmarketing Commitment

- The sponsor should continue collecting blood samples in patients with chronic ITP who receive long term Nplate treatment to test the incidence of binding and neutralizing antibodies to romiplostim and/or to the endogenous thrombopoietin (TPO). The impact of the appearance of these antibodies on clinical efficacy and safety should be assessed.

If it is determined that it is not appropriate to include the long-term immunogenicity testing in the Risk Evaluation and Mitigation Strategy (REMS) Plan, the sponsor should conduct this long-term immunogenicity testing as a postmarketing commitment.

3. Summary of Clinical Pharmacology Review

Introduction: This is a Biologics License Application (BLA) submitted by Amgen for a new molecular entity (NME), romiplostim (Nplate™). The sponsor seeks FDA approval for Nplate for an orphan indication - for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins, and who are splenectomized and have an insufficient response to splenectomy. In support of the proposed indication, the sponsor submitted data obtained from nine clinical studies with two studies in healthy subjects (N=78), four dose-finding studies (n=73), two registration studies (n=125) and one extension study (n=137) in patients with chronic ITP.

Mechanism of Action: Romiplostim is a recombinant protein that binds to the thrombopoietin (TPO or c-Mpl) receptor on blood and bone marrow cells including megakaryocytes, and stimulates platelet production. This mechanism of action is different from existing treatments for ITP, which focus on non-specific immunosuppression to reduce antibody production.

Efficacy Evaluation: The efficacy of Nplate was studied in two registration trials, one in splenectomized patients (N=63) and the other in non-splenectomized patients (N=62). The primary efficacy endpoint was a durable platelet response ($\geq$ 6 weekly platelet count $\geq 50 \times 10^9$/L during last 8 weeks of 24 weeks treatment period, in the absence of rescue medication at any time) compared to placebo. The secondary efficacy endpoints included a transient platelet response (the achievement of any weekly platelet counts $\geq$ 50 x 109/L for any four weeks during the treatment period without a durable platelet response) and an overall platelet response (the achievement of either a durable or a transient platelet

response). Bleeding events were also recorded.

Safety Profile: The most important serious adverse reactions associated with Nplate in clinical studies consisted of bone marrow reticulin deposition and worsening thrombocytopenia after Nplate discontinuation. In the two placebo-controlled registration trials, the most common adverse reactions ($\geq$ 5% higher patient incidence in Nplate versus placebo) are arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia. Headache was the most commonly reported adverse reaction that did not occur at $\geq$ 5% higher patient incidence in Nplate versus placebo. These adverse reactions were mild to moderate in severity. Serious adverse reactions occurred among 14 (17%) patients receiving Nplate and 8 (20%) patients receiving placebo. Nplate treatment also caused various forms of hemorrhage (6 patients) with single occurrences of the following events: bone marrow reticulin deposition, angioneurotic edema, appendicitis, cerebrovascular accident, and B-cell lymphoma.

Risk-Benefit Assessment: This application was discussed at the Oncology Drug Advisory Committee meeting (http://www.fda.gov/ohrms/dockets/ac/cder08.html#pedsub) held on March 12, 2008 and the consensus among the committee members was that the Nplate clinical data demonstrate a favorable risk-benefit profile for certain patients with chronic ITP. Risk management plan should be implemented and Phase 4 studies should be conducted to address the safety concerns related to the long term Nplate therapy in patients with chronic ITP.

Selection of the Initial Dose, Platelet Count Target and Dose Adjustment Guideline: Four dose finding studies were conducted using either a weight-based dose or fixed doses to evaluate the PK and platelet profiles of Nplate in subjects with chronic ITP. Achievement of the target platelet response (defined as the peak platelet count achieving a doubling of baseline platelet and within the range of $\geq 50 \times 10^9$/L and $\leq 450 \times 10^9$/L, in the absence of rescue medication) was dose-dependent. Dose-finding studies identified the starting dose of 1 mcg/kg and weekly dosing schedule based on the patient platelet responses. This initial dose followed by the dose adjustment with increments of 1 mcg/kg based on the platelet count. The most frequently used weekly dose of Nplate for non-splenectomized patients was between 1-3 mcg/kg (25th–75th percentile; median: 2 mcg/kg), and for splenectomized patients was between 2-7 mcg/kg (25th–75th percentile; median: 3 mcg/kg). Since higher platelet count target and higher dose presented higher risk (thrombotic risks, and increased reticulin) in the clinical trials, in the proposed product label dose guideline has been modified to adjust weekly dose by increments of 1 mcg/kg to minimize the risk of bleeding by achieving and maintaining a platelet count $\geq 50 \times 10^9$/L. Do not exceed the maximum weekly dose of 10 mcg/kg. Do not dose if platelet count is ——— Discontinue if platelet count does not increases after 4 weeks at the maximum dose.

Dose-Response Relationships: Both the exposure of romiplostim and the platelet response (PD) are dependent on the dose administered and the baseline platelet count. A linked PK/PD model was developed for romiplostim, which incorporated receptor-

mediated distribution and elimination to describe romiplostim disposition. In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet count. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with chronic ITP, the peak platelet counts were 1.3 to 14.9 times greater than the baseline platelet counts over a 2- to 3-week period. In a study, the platelet counts of patients with chronic ITP who received six weekly doses of 1 mcg/kg Nplate were within the range of 50 to 450 $x10^9$/L for 7 out of 8 patients.

Nplate administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Bone marrow reticulin was observed in 10 of 271 patients exposed to Nplate in clinical studies. Patients who experienced increased bone marrow reticulin received Nplate at higher doses with 6 of these 10 patients at doses greater than or equal to 10 mcg/kg weekly.

Pharmacokinetics (PK) of Romiplostim: The pharmacokinetics of romiplostim were studied in healthy subjects after intravenous Nplate administration. Systemic exposure to romiplostim (C_0 and AUC_{0-t}) increased more than proportionally with dose. This finding was consistent with the target-mediated disposition. Romiplostim presumably binds to c-Mpl on platelets and other cells in the thrombopoiesis lineage, such as megakaryocytes, and is subsequently internalized and degraded inside these cells. The mean elimination half-life was short and increased with dose (1.5, 2.4 and 13.8 hours for doses of 0.3, 1 and 10 mcg/kg, respectively). The characterization of PK in healthy subjects after subcutaneous administration of Nplate was not successful due to non measurable concentrations in most samples after 0.1, 0.3, 1 and 2 mcg/kg doses. In the long-term extension study in patients with chronic ITP who received weekly treatment of Nplate subcutaneously over the dose range of 3 to 15 mcg/kg, peak serum concentrations were observed around 7 to 50 hrs postdose (median: 14 hrs) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum romiplostim is in part dependent on the c-Mpl receptor on platelets. As a result, for a given dose, patients with high platelet counts were associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum romiplostim concentrations was observed after six weekly doses of 3 mcg/kg of Nplate.

Special Population: Of the 271 patients who received Nplate in ITP clinical studies, 38 (19%) were age 65 and over and 18 (9%) were 75 and over. No overall differences in safety or efficacy have been observed between older and young patients in the placebo-controlled studies, but greater sensitivity of some older individuals cannot be ruled out. No hepatic or renal studies have been conducted with Nplate. The safety and effectiveness of Nplate in pediatric patients (< age 18) have not been established. It is not known whether romiplostim is excreted in human milk.

Drug Interactions: No formal drug interaction studies of Nplate have been performed. Nplate may be used with other medical ITP therapies such as corticosteroids, danazol, azathioprine, intravenous (IVIG) and anti-D immunoglobulin. The proposed label recommends monitoring platelet counts when combining Nplate with other ITP medical

therapies. If the patient's platelet count is >50x10^9/L, other medical ITP therapies may be reduced or discontinued.

Immunogenicity: As with all therapeutic proteins, patients may develop antibodies to romiplostim. Patients were screened for immunogenicity to romiplostim using a Biacore-based biosensor immunoassay. This assay is capable of detecting both high and low affinity binding antibodies that bind to romiplostim and cross-react with TPO with approximately 5% of false positive rate. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay. In clinical studies, the incidence of pre-existing antibodies to romiplostim was 8% (17/225) and the incidence of binding antibody development during Nplate treatment was 10% (23/225). The incidence of pre-existing antibodies to endogenous TPO was 5% (12/225) and the incidence of binding antibody development to endogenous TPO during romiplostim treatment was 6% (13/225). Of the patients with positive antibodies to romiplostim and/or to TPO, 1 (0.4%) patient had neutralizing activity to romiplostim and none had neutralizing activity to TPO. The impact of antibody development on the efficacy and safety of Nplate is unknown.

Product Comparability: At the Agency's request, the sponsor conducted a PK and PD comparability study between clinical trial material produced by Process I (P1) and commercial material produced by Process 2 (P2). The PK and PD comparability study was performed in the phase 3 extension phase collecting PD data from subset A and PK data from subset B. Both PK and PD substudies were sequential in design by switching patients at stable doses of Nplate from receiving P1 to P2 material in the PD subset (n=22) and from receiving P2 to P1 material in the PK subset (n=20). The PD comparability was demonstrated with the mean difference of 2.8 x 10^9/L (90% CI: -19.2 to 13.7, P=0.95) in platelet counts in the 30-day periods between P2 and P1 material, approximately 4% higher for the P2 material. The results of PK data between P2 and P1 material did not meet the standard bioequivalence criteria with the point estimate for the mean $AUC_{0\text{-}7days}$ ratio (P2 to P1) of 1.17 (90% confidence interval: 0.98 to 1.41), and the point estimate for the mean C_{max} ratio of 1.33 (90% CI: 1.01 to 1.74). These differences in the $AUC_{0\text{-}7days}$ and C_{max} values may be contributed by the inadequate study design (multiple dose levels with small sample size at each dose level) and/or by the real product difference. Given that no differences between the materials produced by P1 and P2 in the product attributes that would affect product PK profile were found in the *in vitro* product characterization and comparability assessment; the differences in PK observed between P1 and P2 materials did not result in clinical significant differences in platelet responses; and all patients in the phase 3 extension study have been switched to receive the P2 material with continuous collection of efficacy and safety data, it is acceptable to market romiplostim produced by the P2 material.

Why the long-term immunogenicity testing is requested as a Postmarketing Commitment (PMC)? The immunogenicity incidence of romiplostim has not been adequately tested in chronic ITP patients, especially in the long term treatment setting. The impact of the development of antibodies to romiplostim or to the endogenous thrombopoietin (eTPO) on the pharmacokinetics, efficacy and safety of romiplostim

could not be determined due to the limited data. For the subject who tested positive for neutralizing antibodies to romiplostim (subject 310701 in study 20030213) at week 79, severe thrombocytopenia was observed following the discontinuation of Nplate. It appears that the incidence of the antibody development tends to increase as the treatment duration increases. The sponsor should continue collecting blood samples in patients with chronic ITP who receive long term Nplate treatment to test the incidence of binding and neutralizing antibodies to romiplostim and/or to eTPO. The impact of the appearance of these antibodies on clinical efficacy and safety of Nplate should be assessed. If it is determined that it is not appropriate to include the long-term immunogenicity testing in the Risk Evaluation and Mitigation Strategy (REMS) Plan, the sponsor should conduct this long-term immunogenicity testing as a postmarketing commitment.

Why a QT/QTc study in ITP patients is <u>not</u> requested as a Postmarketing Commitment (PMC)? The potential of Nplate treatment on QT interval has not been studied. Romiplostim is an Fc fusion protein (peptibody) with relatively smaller molecular weight (~59 KDa) than that of most of other therapeutic proteins and monoclonal antibodies. The potential effect of romiplostim on the QT interval via on-target and/or off-target mechanisms cannot be ruled out. Given that the potential of Nplate treatment on QT interval was not evaluated during clinical studies in patients with chronic ITP and there are no additional clinical studies planned or ongoing for this proposed orphan indication, the sponsor should address the QT issue during their Nplate development for other indications following the principles described in the ICH E14 guidance (http://www.fda.go/cber/gdlns/iche14qtc.pdf).

Why a pediatric study is <u>not</u> requested as a postmarketing commitment (PMC)? The proposed indication for Nplate is for treatment of chronic ITP which has an orphan designation. Under the Pediatric Research Equity Act (PREA, 2007), orphan indications are exempt from pediatric studies. ITP occurs in adults and pediatric patients with greater prevalence in pediatric population. The manifestations of ITP importantly differ between adults and pediatrics. In adults, ITP frequently results in chronic thrombocytopenia and a risk for life-threatening hemorrhage. In pediatrics, thrombocytopenia frequently resolves spontaneously. Amgen informed the Agency that they are conducting a pediatric study (Study 20060195) with Nplate and will consider further studies upon review of the data from this study.

4. Labeling Recommendation

Please see Clinical Pharmacology recommended labeling modifications in the Clinical Pharmacology primary review by Dr. Yuxin (Angela) Men.

Hong Zhao 04/18/08

Hong Zhao, Ph.D.
Team leader, Clinical Pharmacology Division 5/OCP

NAM Atiqur Rahman 04/18/08

NAM Atiqur Rahman, Ph.D.
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Clinical Pharmacology Review

BLA: 125268	Submission Date(s): 10/29/2007, 1/23/2008, 2/8/2008, 2/22/2008, 3/11/2008; 3/18/2008; 3/21/08; 3/28/08; 4/8/08
Brand Name	Nplate™
Generic Name	Romiplostim
Primary and PM Reviewer	Angela Yuxin Men, M.D., Ph.D.
PM Secondary Reviewer	Yaning Wang, Ph.D.
Team Leader	Hong Zhao, Ph.D.
Division	Clinical Pharmacology V
Clinical Division	Biologic Oncology Product
Sponsor	Amgen
Relevant IND(s)	BB-IND 10205
Submission Type; Code	NME, Priority Review
Formulation; Strength(s)	250 mcg or 500 mcg in single-use vials. Refrigerate lyophilized Romiplostim and protect from light
Proposed Indication	Nplate is a thrombopoietin (TPO) mimetic indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): • Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins. • Who are splenectomized and have an insufficient response to splenectomy.
PDUFA Date	Original: 4/23/08; Extended to 7/23/08

OCP Briefing was held on March 25, 2008 attended by:

Larry Lesko, Shiew-Mei Huang, Nam Atiqur Rahman, Brian Booth, Kelly Renolds, Hong Zhao, Yaning Wang, Jang-Ik Lee, Rafel Rieves, Kathy Robie Suh, Kassa Ayalew, David Frucht, Jonny Lau, Rosane Charlab Orbach, Jeffrey Tworzyanski, Ting Eng Ong, Lucun Bi, Vaidyanathan, Jayabharathi

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EXECUTIVE SUMMARY

1.1 Recommendation

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the sponsor commits to the Phase 4 commitments listed below.

1.2 Phase IV Commitment

- The sponsor should continue collecting blood samples in patients with chronic ITP who receive long term Nplate treatment to test the incidence of binding and neutralizing antibodies to romiplostim and/or to the endogenous thrombopoietin (TPO). The impact of the appearance of these antibodies on clinical efficacy and safety should be assessed.

1.3 Clinical Pharmacology Findings

Introduction: Nplate (Romiplostim) is an Fc fusion protein (peptibody) that increases platelet production via the thrombopoietin (TPO) receptor (also known as cMpl), which activates intracellular transcriptional pathways. The peptibody molecule is comprised of a human immunoglobulin G1 (IgG1) Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing two TPO receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO (eTPO). Romiplostim is produced by recombinant DNA technology in Escherichia coli (E coli).

Romiplostim is being developed as a treatment for thrombocytopenia associated with immune (idiopathic) thrombocytopenic purpura (ITP). Romiplostim has received orphan designation for this proposed indication in major global regions, United States (US) (2003), The sponsor submitted the current BLA seeking the full approval of Romiplostimfor the treatment of ITP and this BLA is under priority review.

The clinical development program included 13 studies, in which nine included clinical pharmacology information. Two pivotal studies were conducted to demonstrate the efficacy of Romiplostim on the durable platelet response.

Pharmacokinetics Findings: Pharmacokinetics (PK) of Romoplostim were studied in both healthy subjects and in patients with chronic ITP.

Healthy Subjects: After a single IV injection, serum exposure to Romiplostim (C_0 and AUC_{0-t}) increased more than proportionally with dose and the initial volume of distribution decreased with dose, indicating that the time-averaged systemic clearance decreased as dose increased. These findings were consistent with the target-mediated

disposition. Romiplostim presumably binds to c-Mpl on platelets and other cells in the thrombopoiesis lineage, such as megakaryocytes, and is subsequently internalized and degraded inside these cells.

ITP Patients: In the long-term extension study in patients with chronic ITP receiving weekly treatment of Romiplostim subcutaneously, over the dose range of 3 to 15 mcg/kg the time to reaching peak serum concentrations ranged from 7 to 50 hours postdose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not proportionally correlate with the dose administered. The elimination of serum Romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed after six weekly doses of Romiplostim at 3 mcg/kg dose (N=4).

The PK results from healthy subjects could not be used to compare to the PK data from ITP patient due to limited PK information obtained in healthy subjects receiving SC injection.

Pharmacokinetics in Specific Populations: No formal PK studies were conducted in subjects with hepatic impairment, renal impairment or in geriatric and pediatric populations. No studies were conducted to evaluate the effect of age, gender and body weight on Romiplostim exposure.

Pharmacodynamic Findings: The primary endpoint of efficacy is durable platelet response, which was defined as a weekly platelet count $\geq 50 \times 10^9$/L for 6 or more times during weeks 18 through 25 in the absence of rescue medication at any time during the treatment period. The overall proportion of subjects who achieved a durable platelet response was 2.4% in the placebo group and 49.4 % in the Romiplostim group. The odds ratio for achieving a durable response was 40.45 for Romiplostim treatment over placebo ($p < 0.0001$).

For splenectomized subjects (Study 20030105), no subjects in the placebo group and 38.1% of the subjects in the Romiplostim group achieved a durable platelet response ($p = 0.0013$); the odds ratio could not be calculated because of the zero value for placebo. For the non-splenectomized subjects (Study 20030212), 4.8% of the subjects in the placebo group and 61.0% of the subjects in the Romiplostim group achieved a durable platelet response; the odds ratio for achieving a durable response was 24.45 for Romiplostim treatment over placebo ($p < 0.0001$).

Age and gender appeared to have no effect on the efficacy endpoint. Although fixed doses demonstrated a dose-response in peak platelet counts after the first dose, the peak platelet count appeared to be lower for subjects who had higher body weight than those who had lower body weight, suggesting that weight-based dosing be a more appropriate dosing strategy to provide treatment for subjects with chroic ITP.

Dose-Response: The PK/PD relationship between Romiplostim dose and platelet counts was established for the healthy subjects. Platelet responses, measured by P_{max}/P_0 and AUC_{plt}/P_0, increased with dose and were similar after IV and SC administration. These results demonstrated that both the exposure of Romiplostim and the PD response are dependent on the dose administered and the baseline platelet counts. A linked PK/PD model was developed for Romiplostim in healthy subjects, which incorporated receptor-mediated distribution and elimination processes to describe Romiplostim disposition.

The PK/PD relationship between Romiplostim dose and platelet counts in ITP patients showed a linear tendency between the baseline normalized platelet count ratio and the dose administrated. The ITP patients are more sensitive to Romiplostim than the healthy subjects.

Selection of Platelet Count Target, Intial Dose and Dose Adjustment: Four dose-finding studies were conducted to evaluate the PK and platelet profiles of Romiplostim in subjects with chronic ITP and to evaluate Romiplostim doses that would increase the platelet counts to a target level, which was defined as the peak platelet count achieving a doubling of baseline platelet counts and within the range of $\geq 50 \times 10^9$/L and $\leq 450 \times 10^9$/L, in the absence of rescue medication.

Achievement of the target platelet response (doubling from baseline and $P_{max} \geq 50 \times 10^9$/L) was dose-dependent. Patients in the 1 μg/kg, 3 μg/kg, and 6 μg/kg cohorts achieved a platelet count $\geq 50 \times 10^9$/L. Thus, 1 μg/kg once weekly was selected as an initial dose. Dose adjustments should be made to achieve and maintain platelet counts $\geq 50 \times 10^9$/L , but the dose should not exceed the maximum weekly dose of 10 mcg/kg.

Immunogenicity: The incidences of antibodies against Romiplostim and TPO were assessed in 235 subjects from 9 ITP clinical studies with 225 subjects received Romiplostim and 10 subjects received only placebo.

The incidence of pre-existing binding antibodies to Romiplostim was 7.5% (17 subjects) and to TPO was 5.3% (12 subjects). The incidence of developing binding antibodies to Romplostim was 10.2% (23 subjects) and to TPO was 5.8% (13 subjects). The incidence of developing neutralizing antibodies to Romiplostim was 0.4% (1 subject) for Romiplostim treatment and none for placebo dosed subjects.

For the subject who tested positive for neutralizing antibodies to Romiplostim (subject 310701 in study 20030213) at week 79, a severe thrombocytopenia was oberserved following the discontinuation of Romiplostim.

The impact of immunogenicity of Romiplostim on the PK, efficacy and safety could not

be determined due to the limited data. As the incidence of antibodies tends to increase in the long-term use of Romiplostim, the Agency requests the sponsor to continue testing the immunogenicity and assessing the impact of immunogenicity on the efficacy and safety of Romiplostim following the long-term use.

Drug Metabolism and In Vivo Drug-Drug Interaction: No studies on the metabolism of Romiplostim have been performed in humans. Metabolism studies are not generally performed for proteins which are degraded into amino acids that are then recycled into other proteins. No drug-drug interaction assessment was performed betwen Romiplostim and other drugs or biologics.

QT/QTc Evaluation: The potential of Nplate treatment on QT interval has not been studied. Romiplostim is an Fc fusion protein (peptibody) with relatively smaller molecular weight (~59 KDa) than that of most of other therapeutic proteins and monoclonal antibodies. The potential effect of romiplostim on the QT interval via on-target and/or off-target mechanisms cannot be ruled out. Given that the potential of Nplate treatment on QT interval was not evaluated during clinical studies in patients with chronic ITP and there are no additional clinical studies planned or ongoing for this proposed orphan indication, the sponsor should address the QT issue during their Nplate [redacted] following the principles described in the ICH E14 guidance (http://www.fda.go/cber/gdlns/iche14qtc.pdf).

Safety Profile: Within the two pivotal clinical studies, the proportion of patients who were reported as having any adverse event was 100% for the Romiplostim group and 95% for the placebo group. Any serious adverse events were reported for 17% for the Romiplostim group and 20% for the placebo group. Four deaths occurred during the two pivotal studies (three in the placebo group and one in the Romiplostim group).

Headache, usually mild or moderate was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving Romiplostim and 32% of patients receiving placebo. The major safety concern from the Romiplostin clinical development program relates predominantly to five items: a) reticulin formation and risk for marrow fibrosis, b) risk for malignancy or progression of malignancy, c) thrombotic risks, d) re-occurrence of thrombocytopenia after cessation of Romiplostim therapy and e) immunogenicity.

Product Comparability: The initial clinical manufacturing process, referred to as P1 for Romiplostim was used in support of phase 1, 2 and pivotal phase 3 clinical trials. The commercial drug substance manufacturing process, referred to as P2, was developed to [redacted] . P2 [redacted] producing drug substance and drug product comparable to P1.

An assessment of PD and PK comparability was done in an open-label extension study

(Study 20030213). The PD comparability was established between P1 and P2 materials, but the PK comparability data did not meet the standard bioequivalence crieteria. The differences in the $AUC_{0\text{-}7days}$ and C_{max} values may be contributed by the inadequate study design (multiple dose levels with small sample size at each dose level) and/or by the real product difference. The differences in PK observed between P1 and P2 materials did not result in clinical significant differences in platelet response. All patients in the phase 3 extension study have been switched to receive the P2 material with continuous collection of efficacy and safety data.

Conclusion: Overall, acceptable Clinical Pharmacology information is presented in this BLA. The pivotal clinical trials demonstrated efficacy of Romiplostim in chronic ITP patients receiving the proposed dose regimen. The risk-benefit of Romiplostim treatment for patients with chronic ITP was discussed at the Oncology Advisory Committee meeting (ODAC) on March 12, 2008 and all committee members (N=10) voted for a favorable benefit of Romiplostim (http://www.fda.gov/ohrms/dockets/ac/cder08.html#pedsub).

Signatures:

4/21/08

Angela Yuxin Men, M.D., Ph.D.
Clinical Pharmacology Reviewer, Biologic Product Team
Division of Clinical Pharmacology V

Hong Zhao 4/21/08

Hong Zhao, Ph.D.
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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Chemistry and Physical-Chemical Properties: Romiplostim, a member of the thrombopoietin (TPO) mimetic class, is an Fc-peptide fusion protein (peptibody). The peptibody molecule is comprised of a human immunoglobulin IgG1 Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing two thrombopoietin receptor-binding domains (Figure 1). The molecular weight is 59 kilodaltons. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in Escherichia coli (E. coli). The physical and chemical properties of Romiplostim are listed in Table 1.

Figure 1. Schematic of AMG 531

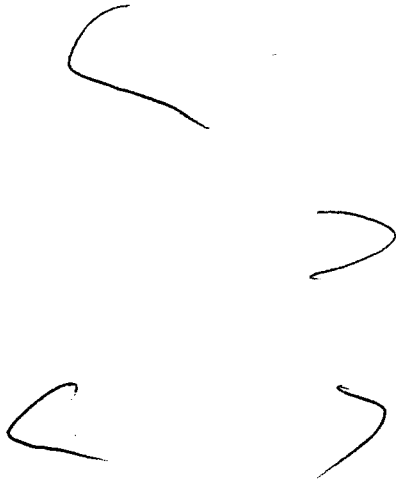


Table 1. Physical and Chemical Properties of AMG 531

Physical or Chemical Property	Description
Theoretical molecular weight	59085 Da

Formulation: Nplate is supplied as a sterile, preservative-free, lyophilized, solid white powder that must be reconstituted with Sterile Water For Injection, USP for subcutaneous injection. Two vial presentations are available, which contain a sufficient amount of active ingredient to provide either 250 mcg or 500 mcg of Romiplostim in 5 mL vials. Each vial of Nplate also contains the following inactive ingredients: L-histidine, sucrose,

mannitol, polysorbate-20, and [redacted]hydrochloric acid to adjust the pH to a target of 5.0.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Mechanism of Action: Romiplostim activates intracellular transcriptional pathways to increase platelet production via the TPO receptor (also known as cMpl). Romiplostim has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Thus, administration of Romiplostim is not expected to elicit immunogenic responses against eTPO.

Proposed Indication: Romiplostim is a TPO mimetic indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP):

- Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins.
- Who are splenectomized and have an insufficient response to splenectomy.

2.1.3 What are the proposed dosage and route of administration?

Proposed Dose and Route of Administration: Romiplostim is administered as a weekly subcutaneous (SC) injection to maintain a platelet count greater than or equal to 50 x 10^9/L. The initial dose for Romiplostim is 1 mcg/kg based on actual body weight.

Dose Adjustments: Adjust the weekly dose of Romiplostim by increments of 1 mcg/kg until the patient achieves a platelet count greater than or equal to 50 x 10^9/L. Assess the platelet count weekly until a stable platelet count (greater than or equal to 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved and monthly thereafter. Do not exceed a maximum weekly dose of 10 mcg/kg.
Discontinue Romiplostim if platelet count does not increase after 4 weeks at the highest weekly dose of 10 mcg/kg.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Romiplostim clinical program consists of 13 clinical studies investigating the clinical pharmacology, pharmacokinetics, safety, efficacy, and quality of life (QoL) in subjects with chronic ITP, myelodysplastic syndromes (MDS), or chemotherapy-induced thrombocytopenia (CIT).

Clinical pharmacology studies (Two studies in healthy subjects and 7 studies in subjects with chronic ITP) are described in Table 2.

Table 2. Romiplostim Clinical Pharmacology Studies

Study Number	Phase	Subjects	Material	Dose[a]; Schedule	Subjects Enrolled	Pharmacokinetics		Pharmacodynamics	
						Sampling Schedule[b]	Subject Number	Sampling Schedule[b]	Subject Number
20000109	1	Healthy	P1	0.3, 1.0, 10.0; SD (IV)[a] 0.1, 0.3, 1.0, 2.0; SD	48	Intensive	32	Intensive	48
20040134	1	Healthy, Japanese	P1	0.3, 1.0, 2.0, 3.0[c]; SD	30	Intensive	8	Intensive	30
20000137A	1/2	ITP	P1	0.2, 0.5, 1.0, 3.0, 6.0, 10.0; ≤ two doses	24	None	0	Intensive	24
20000137B	1/2	ITP	P1	1.0, 3.0, 6.0; QW	21	Intensive	17	Sparse	21
20010218	1/2	ITP	P1	30, 100, 300, 500[d]; ≤ two doses	16	None	0	Intensive	16
20050162	2	ITP, Japanese	P1	1.0, 3.0, 6.0; QW	12	None	0	Sparse	12
20030105	3	ITP, splenectomized	P1	1.0 to 15.0 (dose adjustment); QW	63	Sparse	18	Sparse	63
20030212	3	ITP, non-splenectomized	P1	1.0 to 15.0 (dose adjustment); QW	62	Sparse	10	Sparse	62
20030213	OLE	ITP	P1/P2	1.0 to 10.0[d] (dose adjustment); QW	137	Sparse	14	Sparse	137
Subset A					41[e]	Sparse	41[e]	Sparse	41[e]
Subset B					20	Intensive	20	Sparse	20

ITP = immune (idiopathic) thrombocytopenic purpura
OLE = Open label extension study enrolled subjects from any previous ITP studies conducted in the US/EU
SD = single dose; QW = every week
[a]The dose unit is µg/kg, except for µg unit dosing in Study 20010218; all doses were given by the SC route except for three cohorts in study 20000109 that had AMG531 given by the IV route
[b]Intensive samples were collected to provide PK or PD profiles; sparse samples were collected once weekly or less frequently
[c]The maximum planned doses of 3.0 µg/kg in Study 20040134 was not reached because stopping rules for excess elevation of platelet count were reached at the next lower planned dose.
[d]Subjects on previous studies could carry their doses forward into this study; the maximum dose across previous studies was 30 µg/kg. Subjects who were receiving a dose > 10 µg/kg prior to the amendment were allowed to remain on that dose; however, the subject's dose could not be further increased. If the subject's dose was decreased after enrollment, the dose could not be subsequently increased to > 10 µg/kg.
[e]22 of 41 subjects were qualified for inclusion in the analysis

Two phase 1, single-dose studies were conducted to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of Romiplostim in healthy subjects, including a study in predominantly white subjects (Study 20000109) and a study in Japanese subjects (Study 20040134).

Two dose-finding studies, each with 2 doses of Romiplostim given 2 or 3 weeks apart, were conducted in subjects with chronic ITP to explore dosing frequency and to evaluate the PD effects of Romiplostim with a weight-based dosing (Study 20000137A) and a fixed-dose administration (Study 20010218). The PK and PD of Romiplostim with the once-weekly, weight-based dosing in subjects with ITP were evaluated in 2 additional dose-finding studies in predominantly white (Study 20000137B) and Japanese (Study 20050162) populations.

Limited trough PK samples were collected from 2 pivotal trials (Study 20030105 and Study 20030212) and an open-label extension study (Study 20030213) in subjects with ITP to support safety assessments. Two subset studies were conducted in subjects with ITP participating in the open-label study to assess the PD comparability and other study endpoints (Study 20030213-Subset A) and the PK comparability of the Process 1 (P1) and Process 2 (P2) materials (Study 20030213-Subset B).

2.2.2 What is the basis of the dose selection?

Four dose-finding studies (137A, 137B, 218 and 162) were conducted to evaluate the PK and platelet profiles of Romiplostim in subjects with ITP and to evaluate Romiplostim doses that would increase the platelet counts to a target level which was defined as the peak platelet count achieving a doubling of baseline platelet counts and within the range of $\geq 50 \times 10^9$/L and $\leq 450 \times 10^9$/L, in the absence of rescue medication.

Study 20000137A showed that Romiplostim caused an apparent dose-dependent increase in platelet counts in subjects with ITP, with target platelet counts achieved in some subjects in the 3.0, 6.0, and 10.0 mcg/kg cohorts. A majority (83%) of subjects were administered the second dose 2 weeks after the first dose because the platelet count were below 50 x 10^9/L, suggesting that more frequent dosing than every 2 weeks is required to achieve and/or maintain platelet counts in a therapeutic range.

Study 20010218, a phase 2 study assessed the safety and efficacy of unit doses (30, 100, 300, and 500 mcg SC) of Romiplostim in subjects with ITP, showed that the peak platelet count appeared to be lower for subjects who had higher body weight than those who had lower body weight. This finding suggests that weight-based dosing may be a more appropriate dosing strategy to provide treatment for subjects with ITP.

Study 20000137B is a double-blind, randomized, placebo-controlled, parallel-group study designed to assess weekly dosing of Romiplostim at doses previously identified from Study 20000137A as tolerable and capable of increasing platelet counts (ie, 1.0, 3.0, and 6.0 mcg/kg). Mean weekly platelet counts increased in a dose-dependent manner after administration of Romiplostim (Figure 2).

These results supported the use of 1.0 µg/kg as the starting dose for weekly administration of Romiplostim in later studies in subjects with ITP, with the inclusion of individual dose-adjustment guidelines.

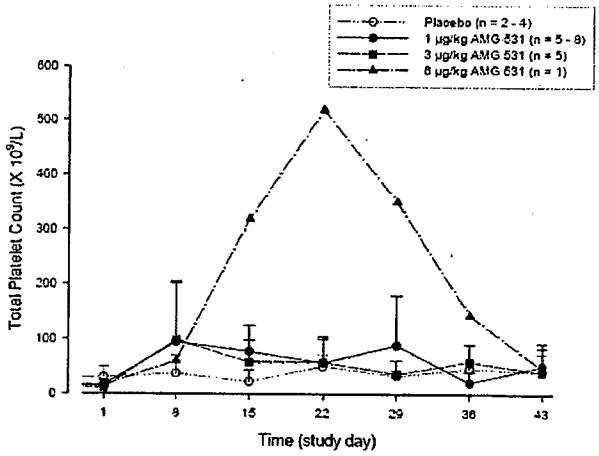


Figure 2. Total Platelet Count vs. Time (Study 2000137B)

Study 20050162 is a phase 2 study to evaluate the safety and efficacy of Romiplostim administered SC once weekly in Japanese subjects with ITP. Achievement of the target platelet response was dose-dependent. Comparing the platelet response in the 1 mcg/kg cohort to that in the 3 mcg/kg cohort, treatment with 3 µg/kg provided a more robust response without exceeding 450 x 10^9/L and, therefore, was selected for a planned phase 3 study in thrombocytopenic Japanese subjects with ITP.

By comparing the platelet count results obtained from the Caucasian (Study 137) and the Janpanese (Study 162) (Figure 3), the Caucasian is more sensitive to Romiplostim than the Janpanese. However, the reason for this difference is not clear.

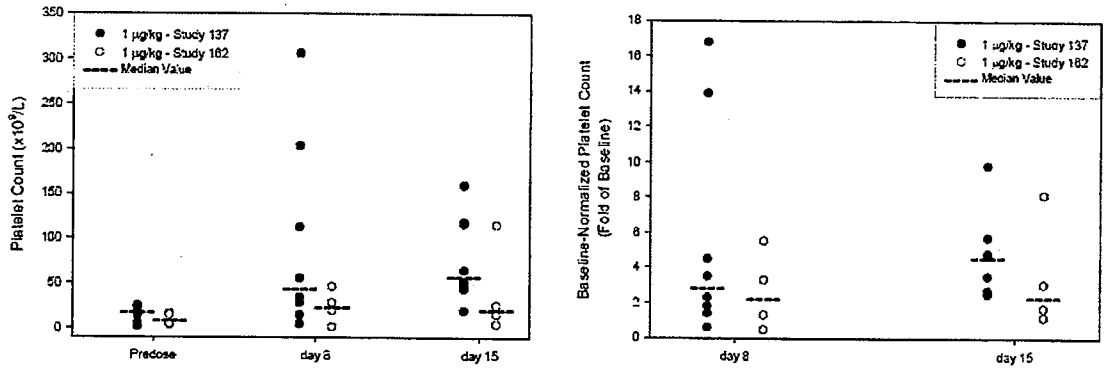


Figure 3. Comparison of the Platelet Counts between Study 137 and Study 162

2.2.3 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of safety and efficacy?

Efficacy: Two pivotal clinical studies provide efficacy results of Romiplostim among patients with chronic ITP. Study 20030212 enrolled patients who had not undergone splenectomy and Study 20030105 enrolled patients who were refractory to splenectomy, These studies used randomized (2:1; active: placebo), double-blind, placebo controlled designs with the enrollment of patients who were thrombocytopenic despite prior therapy with at least one prior ITP medication. Patients were exposed to the study drug for six months with weekly measurement of platelet counts. At the end of the study, patients were observed for another 12 weeks without administration of the study drug.

The primary endpoint of efficacy is durable platelet response, which was defined as a weekly platelet count $\geq 50 \times 10^9$/L for 6 or more times during weeks 18 through 25 in the absence of rescue medication at any time during the treatment period. The major secondary endpoints included various comparisons of platelet count responses (defined as any weekly platelet count $\geq 50 \times 10^9$/L) and comparison of the use of thrombocytopenia "rescue medications."

Romiplostim was statistically significantly superior to placebo for the primary and secondary efficacy endpoints of platelet response in the pivotal phase 3 studies, 20030105 and 20030212 (Figure 4, Table 3).

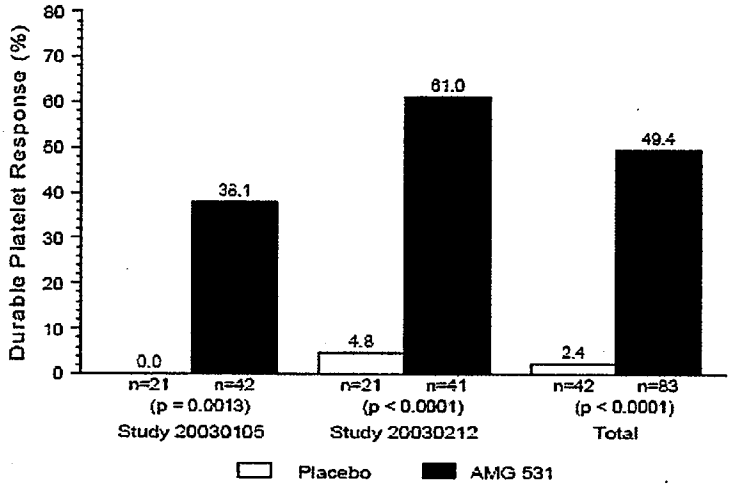


Figure 4. Incidence of Durable Platelet Response (Phase 3 Studies)

Table 3. Summary Results of the Primary and Secondary Endpoints

Outcome	Study 20030105 (splenectomy)		Study 20030212 (no splenectomy)		p-value
	Placebo n = 21	Romiplo-stim n = 42	Placebo n = 21	Romiplo-stim n = 41	
Durable platelet response, n (primary EP)	0 (0%)	16 (38%)	1 (5%)	25 (61%)	< 0.01
Major secondary Endpoints					
Overall platelet response, n	0 (0%)	33 (79%)	3 (14%)	36 (88%)	< 0.01
Weeks with platelet response, mean (SD)	0.2 (0.5)	12.3 (7.9)	1.3 (3.5)	15.2 (7.5)	< 0.01
Subjects requiring rescue medication, n	12 (57%)	11 (26%)	13 (62%)	7 (17%)	< 0.01
Subjects with durable platelet response with "stable dose", n	0 (0%)	13 (31%)	0 (0%)	21 (51%)	< 0.01

When the results of the pivotal phase 3 studies were combined, the overall proportion of subjects who achieved a durable platelet response was 2.4% in the placebo group and 49.4 % in the Romiplostim group. The odds ratio for achieving a durable response was 40.45 for Romiplostim treatment over placebo ($p < 0.0001$).

For splenectomized subjects (Study 20030105), no subjects in the placebo group and 38.1% of the subjects in the Romiplostim group achieved a durable platelet response ($p = 0.0013$); the odds ratio could not be calculated because of the zero value for placebo. For the non-splenectomized subjects (Study 20030212), 4.8% of the subjects in the placebo group and 61.0% of the subjects in the Romiplostim group achieved a durable platelet response; the odds ratio for achieving a durable response was 24.45 for Romiplostim treatment over placebo ($p < 0.0001$).

Safety: The Romiplostim safety database consists of information from 204 patients with chronic ITP who were exposed to the product. The two phase 3 clinical studies provide the placebo-comparative information (Table 4). Within these two studies, the proportion of patients who were reported as having any adverse events was 100% for the Romiplostim group and 95% for the placebo group. Any serious adverse events were reported for 17% for the Romiplostim group and 20% for the placebo group. Four deaths occurred during the two studies (3 in the placebo group and one in the Romiplostim group).

Table 4. Adverse Events in Phase 3 Studies

Adverse Event	Placebo (N=41)	Romiplostim (N=84)
Any	39 (95%)	84 (100%)
Any Serious	8 (20%)	14 (17%)
Fatal	3 (7%)	1 (1%)
Any Bleed	25 (61%)	48 (57%)
Any Serious Bleed	4 (10%)	5 (6%)

Headache was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving Romiplostim and 32% of patients receiving placebo. Headaches were usually mild or moderate. Table 5 presents adverse drug reactions from Study 105 and Study 212 (n = 125) with a $\geq$ 5% higher patient incidence in Romiplostim group versus placebo group. The majority of these adverse drug reactions were mild to moderate in severity.

Table 5. Adverse Drug Reactions ($\geq$ 5%) Identified in Two Pivotal Studies

Preferred Term	Nplate n = 84	Placebo n = 41
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in Extremity	13%	5%
Abdominal Pain	11%	0%
Shoulder Pain	8%	0%
Dyspepsia	7%	0%
Paresthesia	6%	0%

The major safety concern from the clinical development program relates predominantly to five items: a) reticulin formation and risk for marrow fibrosis, b) risk for malignancy or

progression of malignancy, c) thrombotic risks, d) re-occurrence of thrombocytopenia after cessation of Romiplostim therapy and e) immunogenicity.

2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to IV, F, Analytical Section; if no, describe the reasons)

Yes. Romiplostim concentrations in serum were measured with an ELISA method to assess PK parameters.

2.2.5 Exposure-response

2.2.5.1 **What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

The PK/PD relationship between serum Romiplostim dose/exposure and platelet counts was established in the healthy subjects. Platelet responses, measured by P_{max}/P_0 (Figure 5) and AUC_{plt}/P_0 (Figure 6), increased with dose and were similar after IV and SC administration.

P_0 = baseline platelet count; P_{max} = the maximum observed platelet count; $t_{max\text{-}plt}$ = the time after initiation of dosing at which P_{max} was observed; AUC_{plt} = area under the platelet count-time profile; AUC_{plt}/P_0 = baseline-normalized AUC_{plt}.

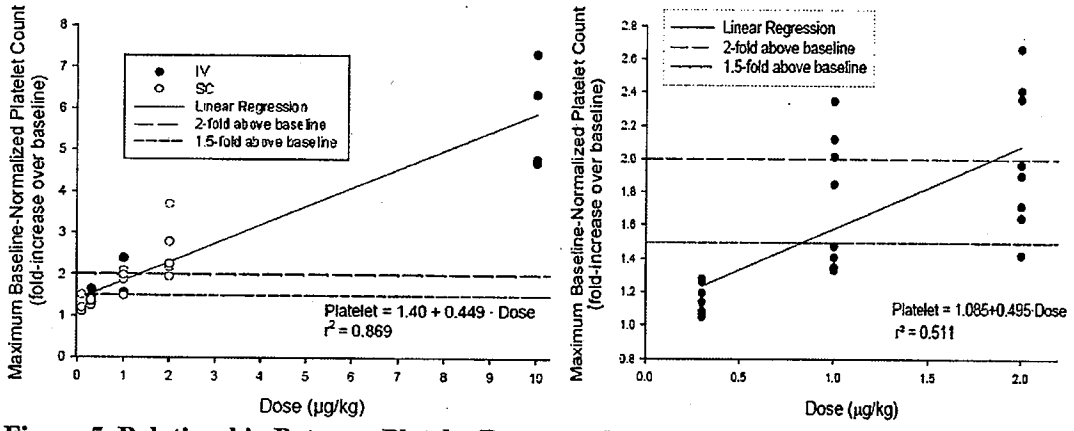


Figure 5. Relationship Between Platelet Response (P_{max}/P_0) and Romiplostim Dose After Single Administration of Romiplostim in Healthy Subjects (Left panel: Study 20000109; Right panel: Study 20040134)

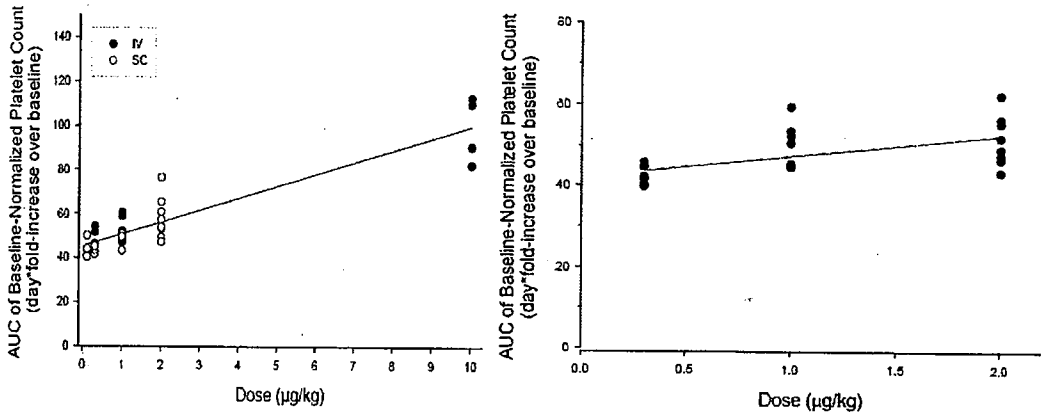


Figure 6. Relationship Between Platelet Response (AUC_{plt}/P_0) and Romiplostim Dose After Single Administration of Romiplostim in Healthy Subjects (L: Study 20000109; R: Study 20040134)

The relative PD response is dependent not only on the Romiplostim dose but also on the baseline platelet count. A linked PK/PD model was developed for Romiplostim in healthy subjects, which incorporated receptor-mediated distribution and elimination processes to describe Romiplostim disposition. These results also showed that the White are more responsive to Romiplostin in platelet response than that in Japanese. However, the reason is unknown.

The PK/PD relationship between serum Romiplostim dose and platelet counts in ITP patients is shown in Figure 7. There is a linear trendency between the baseline normalized platelet count ratio and the dose administrated. Figure 7 also showed that the ITP patients are more sensitive to Romiplostim in platelet response than the healthy subjects.

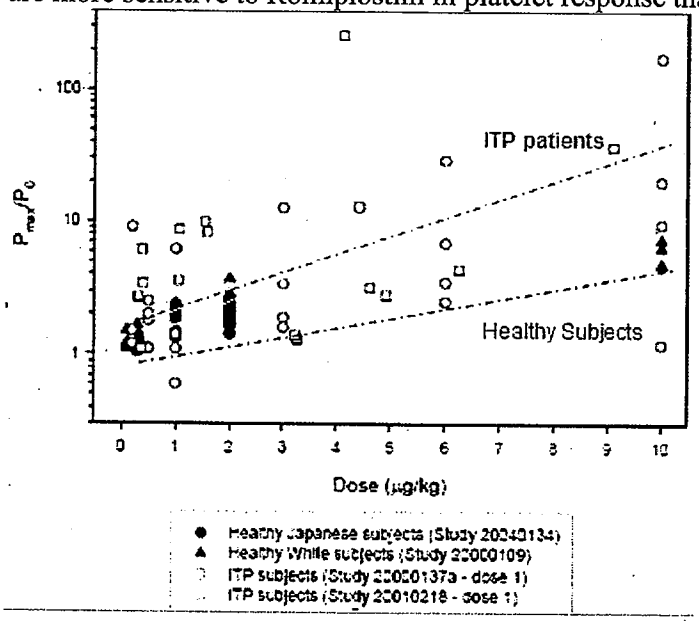


Figure 7. Platelet Count P_{max}/P_0 vs. Dose Administrated

In the phase 3 studies in ITP, the maximum Romiplostim weekly dose allowed was 15 mcg/kg. In the open-label extension Study 20030213, the maximum weekly dose was reduced to 10 mcg/kg based on analyses indicating that no additional clinical benefit (platelet count response) was achieved at doses above 10 mcg/kg/week, and thus the excess exposure for subjects was unnecessary.

While it is recognized that the durable responses in the pivotal studies support lower doses (≤ 7 mcg/kg), other efficacy endpoints as well as data from additional studies indicate that higher Romiplostim doses (8 to 10 mcg/kg) provide clinical benefit to a significant proportion of subjects, particularly those patients who may be extensively pretreated patients with refractory disease. For some pivotal study subjects who did not achieve a durable platelet response, benefit was still obtained in terms of transient response, a component of overall response. Transient response was a key secondary efficacy endpoint, and was defined as at least 4 weekly platelet responses in the absence of any rescue medication during the last 8 weeks. Overall response was the sum of durable plus transient response.

- In Study 20030105 (splenectomized subjects), 73.8% of subjects achieved an overall response in the study (up to 10 mcg/kg), whereas 69.1% of subjects achieved an overall response at doses ≤ 7 mcg/kg. Therefore, approximately 5% of Romiplostim's benefit in terms of this endpoint was achieved at doses higher than 7 mcg/kg/week (Figure 8).
- In Study 20030212 (non-splenectomized subjects), 80.5% of subjects achieved overall responses at doses ≤ 7 mcg/kg; with a maximum dose of 10 mcg/kg, the incremental benefit was approximately 5% (Figure 8).

As shown in Figure 8 and Table 6, the phase 3 study data support additional benefit at doses from 8 to 10 mcg/kg per week in terms of overall response.

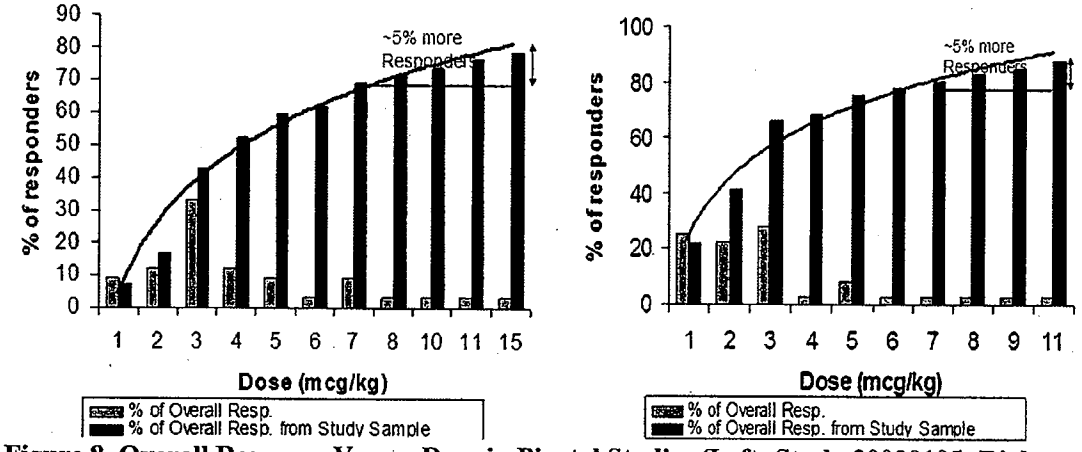


Figure 8. Overall Response Versus Dose in Pivotal Studies (Left: Study 20030105; Right: Study 20030212)

Table 6. Overall Response Versus Dose in Pivotal Studies

Maximum Dose (µg/kg)	No. Overall Responders	% of Overall Responders	Cumulative % of Overall Responders	Cumulative % of Overall Responders From Study Sample
Study 20030105				
1	3	9.09%	9.09%	7.15%
2	4	12.12%	21.21%	16.67%
3	11	33.33%	54.55%	42.87%
4	4	12.12%	66.67%	52.40%
5	3	9.09%	75.76%	59.55%
6	1	3.03%	78.79%	61.93%
7	3	9.09%	87.88%	69.07%
8	1	3.03%	90.91%	71.45%
10	1	3.03%	93.94%	73.84%
11	1	3.03%	96.97%	76.22%
15	1	3.03%	100.00%	78.60%
	33/42 (78.6%)			
Study 20030212				
1	9	25.00%	25.00%	21.95%
2	8	22.22%	47.22%	41.46%
3	10	27.78%	75.00%	65.85%
4	1	2.78%	77.78%	68.29%
5	3	8.33%	86.11%	75.61%
6	1	2.78%	88.89%	78.04%
7	1	2.78%	91.67%	80.48%
8	1	2.78%	94.44%	82.92%
9	1	2.78%	97.22%	85.36%
11	1	2.78%	100.00%	87.80%
	36/41 (87.8%)			

2.2.5.2 **What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

The safety database indicates that Romiplostim administration was associated with increased reticulin in approximately 4% (9/219) of exposed subjects. Two patients had "localized collagen" detected, in addition to the reticulin deposition. Follow-up marrow results are available for five of the nine patients. Two patients had improved reticulin findings and three had stable reticulin findings, all following Romiplostim discontinuation. All of these nine patients had undergone splenectomy and all received "high" doses of Romiplostin ranging from 7 to 18 mcg/kg. However, due to the limited data, the dose-responose for safety of Romiplostim could not be established.

2.2.5.3 **Does this drug prolong the QT or QTc interval?**

The potential of Nplate treatment on QT interval has not been studied. Romiplostim is an Fc fusion protein (peptibody) with relatively smaller molecular weight (~59 KDa) than that of most of other therapeutic proteins and monoclonal antibodies. The potential effect

of romiplostim on the QT interval via on-target and/or off-target mechanisms cannot be ruled out. Given that the potential of Nplate treatment on QT interval was not evaluated during clinical studies in patients with chronic ITP and there are no additional clinical studies planned or ongoing for this proposed orphan indication, the sponsor should address the QT issue [redacted] following the principles described in the ICH E14 guidance (http://www.fda.go/cber/gdlns/iche14qtc.pdf).

2.2.6 Pharmacokinetic characteristics of the drug and its major metabolites.

2.2.5.1 **Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?**

Healthy Subjects

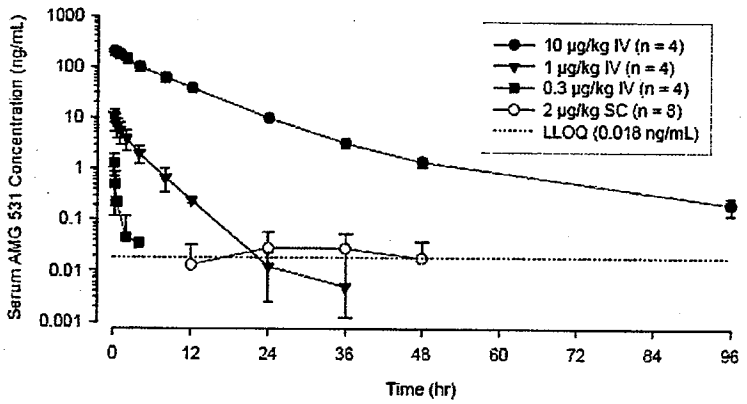
Two PK studies were conducted in healthy subjects. Both of them were single-ascending dose studies following IV and/or SC injection (Study 20000109 and 20040134).

Study 20040134

PK samples were only collected from the 2.0 μg/kg cohort because results from Study 20040134 indicated that serum Romiplostim concentrations were not measurable for SC doses ≤ 1.0 μg/kg. Only 2 of 8 subjects in the 2.0 μg/kg cohort had serum Romiplostim concentrations above the LLOQ. The available PK data (6 data points in total) were not sufficient for PK parameter estimation by noncompartmental analysis.

Study 20000109

The mean Romiplostim serum concentration-time profiles after IV administration are presented in Figure 9. After a single IV dose, systemic exposure to Romiplostim (C_0 and AUC_{0-t}) increased more than proportionally with dose and the initial volume of distribution decreased with dose (Table 7), indicating that the time-averaged systemic clearance decreased as dose increased. These findings were consistent with the target-mediated disposition; Romiplostim presumably binds to c-Mpl on platelets and other cells in the thrombopoiesis lineage, such as megakaryocytes, and is subsequently internalized and degraded inside these cells.



Note: In the 2 µg/kg SC cohort, all concentration values were below the LLOQ in 3 subjects, and these values were set to zero to derive the mean values presented in the graph. All concentration values for the 0.1, 0.3 and 1.0 µg/kg SC cohorts were below the LLOQ.

Figure 9. Mean (SD) Concentration-Time Profiles of Romiplostim after Single IV or SC Administration of Romiplostim in Healthy Subjects (Study 20000109)

Table 7. Noncompartmental PK Parameter Values After Single IV or SC Administration of Romiplostim in Healthy Subjects (Study 20000109)

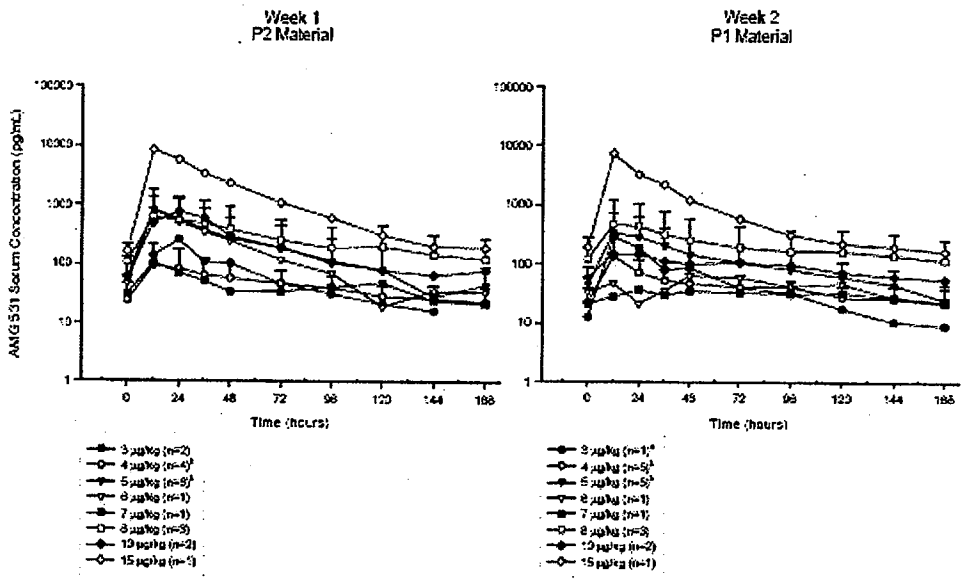
	IV			SC
Parameter	0.3 µg/kg (n = 4)	1.0 µg/kg (n = 4)	10.0 µg/kg (n = 4)	2.0 µg/kg[a] (n = 8)
C_0 or C_{max} (pg/mL)	2810 (1170)	12900 (1760)	211000 (32000)	29.9 (29.0)
t_{max} (h)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.25)	24.0 (24.0-36.0)
AUC_{0-t} (pg-h/mL)	669 (732)	26500 (19000)	1520000 (260000)	1350 (1710)
V_c (mL/kg)	122 (50.6)	78.8 (10.7)	48.2 (7.42)	NA
$t_{1/2}$ (h)	1.50 (2.83)	2.41 (1.56)	13.8 (3.89)	NC

After SC administration, serum Romplostim concentrations were not measurable for all subjects at all timepoints in the 0.1, 0.3, and 1.0 µg/kg cohorts. At 2.0 mcg/kg, serum concentrations of Romiplostim were not measurable at any timepoints for 3 out of 8 subjects and were measurable at the earliest 12 hours postdose and only up to 48 hours postdose for the other 5 subjects. After SC administration, peak concentrations were observed between 24 and 36 hours after dosing. As only partial PK profiles were observed in these 5 subjects, $t_{1/2}$ and absolute bioavailability could not be estimated.

ITP Patients

In Study 20030105, 7 of 8 PK samples collected from 8 subjects who received Romplostim had measurable trough concentrations ranging from ——— pg/mL. In Study 20030212, 3 of 4 PK samples collected from 4 subjects who received Romplostim had measurable concentrations ranging from ——— pg/mL. In Study 20030213, 7 of 16 PK samples collected from 14 subjects who received Romplostim had measurable concentrations ranging from ——— pg/mL. No PK analysis and interpretation were made because the concentration data were limited and doses varied among the subjects.

In the PK comparability study (Study 20030213 B), each individual subject administered the same dose of Romiplostim of the P2 and P1 materials in the following sequence: P2 material on week 1 (day 1) followed by P1 material on week 2 (day 8). A total of 19 PK samples were collected from each subject over 14 days. The doses of Romiplostim ranged from 3 to 15 mcg/kg. The serum concentration-time profiles of Romiplostim are presented in Figure 10. Non-linear PK was demonstrated in Figure 11. After SC administration of the P1 and P2 materials, maximum serum Romiplostim concentrations were observed at a median t_{max} of 14 hours (range = 6.9 to 50 hours) with estimated elimination half-life values ranging from 1 to 34 days (median: 3.5 days). Romiplostim $AUC_{0\text{-}7day}$, C_{max}, and predose platelet counts for each subject are presented in Table 8.



[a] Subject 301951 had thawed samples for 6 of the week 2 samples and were not analyzed.
[b] Subject 303232 had a switch in dose from week 1 to week 2.

Figure 10. Mean (SD) Romiplostim Concentration-Time Profiles for the P1 and P2 Materials (Study 20030213-Subset B)

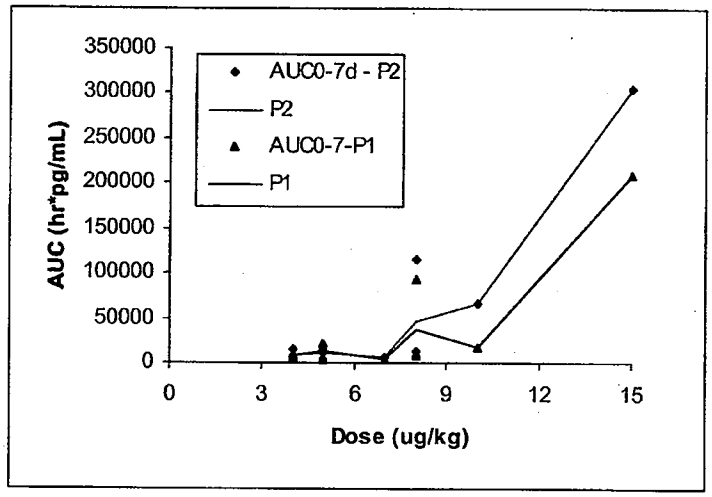


Figure 11. Plots of $AUC_{0\text{-}7day}$ vs. Dose for the P1 and P2 Materials (Study 20030213-Subset B)

Table 8. Romiplostim Pharmacokinetic Parameters and the Predose Platelet Counts by Dose of Romiplostim (Study 20030213-Subset B)

Subject ID	Dose	$AUC_{0\text{-}7day}$ (pg-hr/mL)		C_{max} (pg/mL)		Predose Platelet Counts (x 10^9/L)	
		Week 1	Week 2	Week 1	Week 2	Week 1	Week 2
	(µg/kg)	(P2)	(P1)	(P2)	(P1)		
301933	3	16900[a]	10900[a]	475	296	209	287
301951	3	2970	—[b]	37.8	—[b]	304	216
300531	4	—[c]	—[c]	—[c]	—[c]	194	131
300532	4	6240	6830	45.1	56.0	144	99.0
301957	4	8880	9400	71.8	90.8	195	84.0
305351	4	14500	7180	289	124	124	151
300108	5	117000[d]	46300[d]	2570	1000	31.0	203
300552	5	11700	21400	192	303	131	104
301232	5	10400	4830	162	52.4	102	144
301932	5	18800	18900	390	338	99.0	94.0
303232	5/4[e]	41200	11800	1630	436	267	332
306050	5	5040	5090	94.3	67.2	257	326
309651	6	29800[a]	6550[a]	804	64.4	68.0	215
305930	7	7290	5260	105	37.1	100	333
305330	8	13700	8660	197	74.2	37.0	115
305353	8	117000	94100	1510	1310	74.0	74.0
306054	8	12400	10400	149	88.5	182	214
300121	10	10400[a]	12700[a]	119	181	19.0	22.0
304930	10	66300	18300	1440	159	78.0	152
301201	15	305000	209000	8580	7550	5.00	5.00

[a]Reported $AUC_{0\text{-}6day}$ due to missing samples in 1 of 2 weeks
[b]Week 2 parameters were not reported for Subject 301951 because samples were mishandled
[c]All samples from subject 300531 were below LLOQ (15 pg/mL)
[d]Reported $AUC_{0\text{-}6day}$ due to missing samples in 1 of 2 weeks
[e]Subject 303232 had a switch in dose from 5 µg/kg (week 1) to 4 µg/kg (week 2)

Among these 20 patients listed in Table 8, four (301933, 300108, 306050 and 305930) of them showed positive anti-Romiplostim antibodies, in which patients 301933 and 306050 with pre-existing antibodies to Romiplostim and patients 300108 and 305930 with a developing antibody response. Due to the limited data, it is not feasible to determine the PK difference between patients with positive and negative antibodies.

2.2.5.2 **Do PK parameters change with time following chronic dosing?**

There is not enough PK data to evaluate whether the PK changes with time following chronic dosing. A limited PK data (Study 20000137B) in ITP patients indicated high intersubject variability. In general, the Romiplostim concentrations after the last dose were lower than those after the first dose, which was possibly related to the accelerated removal of Romiplostim as a result of the increased platelet counts over time with Romiplostim treatment (Figure 12).

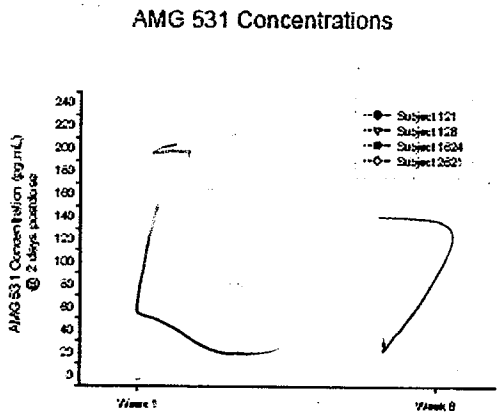


Figure 12. Comparison of Serum Romiplostm Concentrations from Week 1 and Week 6 After Weekly SC Administration of Romiplostim at 3 mcg/kg in Subjects with ITP (Study 20000137B)

2.2.5.3 **How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

Very limited PK information was obtained in healthy subjects following SC administration of Romiplostim, which made an adequate or even an approximate comparison of Romiplostim PK between the healthy subjects and ITP patients not possible.

2.2.5.4 **Is this a high extraction ratio or a low extraction ratio drug?**

Not applicable because Romiplostim is not a small molecule drug but an Fc fusion protein – a peptibody.

2.2.5.5 **Does mass balance study suggest renal or hepatic the major route of elimination?**

No mass balance study has been conducted for Romiplostim. Romiplostim is an Fc fusion protein. Mass balance studies are not generally performed for proteins because they are degraded into amino acids that then recycled into other proteins.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Pharmacokinetics in Special Populations: No dedicated studies were conducted in subjects with hepatic impairment, renal impairment or in geriatric and pediatric populations. Clinical studies of Romiplostim did not include a sufficient number of

healthy subjects and subjects with ITP at each dose level to determine the effects of demographic factors such as sex, age and body weight on Romiplostim exposure.

2.3.1.1 **Age**

Based on the limited available data, age does not appear to have an effect on the primary efficacy endpoint, durable platelet response (Table 9).

Table 9. Incidence of Durable Platelet Response by Age in Pivotals Studies (N1/N2 (%)

Age	Study 20030105		Study 20030212		Total	
	Pacebo (N=21)	Romiplostim (N=42)	Pacebo (N=21)	Romiplostim (N=41)	Pacebo (N=42)	Romiplostim (N=83)
<65	0/16 (0)	13/32 (41)	0/13 (0)	22/33 (67)	0/29 (0)	35/65 (54)
≥65	0/5 (0)	3/10 (30)	1/8 (12.5)	3/8 (38)	1/13 (8)	6/18 (33)
<75	0/21 (0)	14/38 (37)	1/16 (6)	22/35 (63)	1/37 (3)	36/73 (49)
≥75	0	2/4 (50)	0/5 (0)	3/6 (50)	0/5 (0)	5/10 (50)

The proposed indication for Nplate is for treatment of chronic ITP which has an orphan designation. Under the Pediatric Research Equity Act (PREA, 2007), orphan indications are exempt from pediatric studies. ITP occurs in adults and pediatric patients with greater prevalence in pediatric population. The manifestations of ITP importantly differ between adults and pediatrics. In adults, ITP frequently results in chronic thrombocytopenia and a risk for life-threatening hemorrhage. In pediatrics, thrombocytopenia frequently resolves spontaneously. Amgen informed the Agency that they are conducting a pediatric study (Study 20060195) with Nplate and will consider further studies upon review of the data from this study.

2.3.1.2 **Gender**

Based on the limited available data, gender does not appear to have an effect on the primary efficacy endpoint, durable platelet response (Table 10).

Table 10. Incidence of Durable Platelet Response by Gender in Pivotals Studies (N1/N2 (%)

Gender	Study 20030105		Study 20030212		Total	
	Pacebo (N=21)	Romiplostim (N=42)	Pacebo (N=21)	Romiplostim (N=41)	Pacebo (N=42)	Romiplostim (N=83)
Male	0/10 (0)	5/15 (33)	1/5 (20)	9/14 (64)	1/15 (7)	14/29 (48)
Female	0/11 (0)	11/27 (41)	0/16 (0)	16/27 (59)	0/27 (0)	27/54 (50)

2.3.1.3 **Race**

There were too few non-white subjects enrolled in the clinical studies to allow a meaningful analysis.

2.3.1.4 **Body Weight**

Study 20010218 was an open-label, fixed dose, dose-finding (30, 100, 300, and 500 μg, SC) study evaluating the safety and efficacy of Romiplostim in ITP patients. The relationship between baseline-corrected maximum platelet count and body weight is shown in Figure 13. Although fixed doses demonstrated a dose response in peak platelet counts after the first dose, the peak platelet count appeared to be lower for subjects who had higher body weight than those who had lower body weight, suggesting that weight-based dosing be a more appropriate dosing strategy to provide treatment for subjects with ITP.

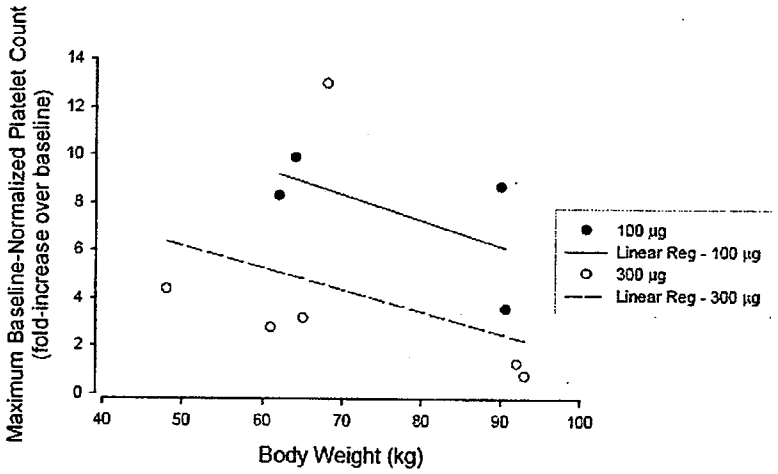


Figure 13. Relationship Between Baseline-corrected Maximum Platelet Count and Body Weight (Study 20010218)

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Dose adjustment is recommended based on the PD parameter - platelet count, not on the exposure-response relationship. The initial dose for Romiplostim is 1 mcg/kg based on actual body weight. Dosage regimen is adjusted weeekly by increments of 1 mcg/kg until the patient achieves a platelet count greater than or equal to 50 x 10^9/L. Assess the platelet count weekly until a stable platelet count achieved (greater than or equal to 50 x 10^9/L) for at least 4 weeks without dose adjustment and monthly thereafter. Do not

exceed a maximum weekly dose of 10 mcg/kg.
Use the body weight at initiation of therapy for all dose calculations. Adjust the dose as follows:

- If platelet count is < 50 x 10^9/L, increase the dose by 1 mcg/kg.
- If platelet count is > 400 x 10^9/L, do not dose. Assess platelet count weekly. After the platelet count has fallen to < 200 x 10^9/L, resume Romiplostim at a dose reduced by 1 mcg/kg.

Discontinue Romiplostim if platelet count does not increase after 4 weeks at the highest weekly dose of 10 mcg/kg.

2.3.2.1 **What pregnancy and lactation use information is there in the application?**

2.3.2.2 **Other factors that are important to understand the drug's efficacy and safety**

Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. The immunogenicity of Romiplostim has been evaluated using two different screening immunoassays for the detection of anti-Romiplostim antibodies, an acid dissociation bridging enzyme linked immunosorbent assay (ELISA) (detecting high-affinity antibodies) and biosensor immunoassay. This latter assay is capable of detecting both high and low-affinity antibodies that bind to Romiplostim and cross-react with TPO. The results are shown in Table 11.

TABLE 11: Incidence of Anti-Romiplostim Antibodies

Study	Placebo					Romiplostim				
	N	Abs to Romiplostim at pre-dose	Abs to Romiplostim at post-dose	Abs to TPO at pre-dose	Abs to TPO at postdose	N	Pre-existing Abs to Romiplostim	Developing Abs to Romiplostim	Pre-existing Abs to TPO	Developing Abs to TPO
20000137 A						24	2 (8.3)	0	0	0
20000137 B	4	0	0			17	0	0	0	0
20010218						16	0	0	1 (6.3)	0
20050162						12	0	0	0	0
20040209						28	1 (3.6)	3 (10.7)	1 (3.6)	2 (7.1)
20060131						10	1 (10)	1 (10)	0	1 (10)
20030213						34 (107)	9 (6.4)	15 (10.6)	6 (4.3)	8 (5.7)
20030105	21	2 (9.5)		2(9.5)		42	4 (9.5)	1 (2.4)	3 (7.1)	0
20030212	20	2 (10)		4 (20)		42	1 (2.4)	3 (7.1)	2 (4.8)	2 (4.8)
Total	45	4 (8.9%)		6 (13.3%)		225	17(7.5%)	23 (10.2)	12 (5.3)	13 (5.8%)

A total of 311 subjects were evaluated for the development of antibodies to Romiplostim or TPO across 12 clinical studies. In the 2 healthy subject studies (20000109 and 20030134), 78 healthy subjects (22 on placebo and 56 on Romiplostim) were tested for antibodies against Romiplostim and/or TPO.

The incidences of antibodies against Romiplostim and TPO were assessed in 235 subjects from 8 ITP clinical studies; 225 subjects received Romiplostim at some point, while 10 subjects received only placebo.

The incidence of pre-existing binding antibodies to Romiplostim was 7.5% (17 subjects) and to TPO was 5.3% (12 subjects). The incidence of pre-existing neutralizing antibodies to TPO was 0.5% (1 subject) and to Romiplostim was none. The incidence of developing binding antibodies to Romplostim was 10.2% (23 subjects) and to TPO was 5.8% (13 subjects). The incidence of developing neutralizing antibodies to Romiplostim was 0.5% (1 subject) for Romiplostim treatment and none for placebo dosed subjects.

One subject was positive for neutralizing antibodies to Romiplostim (subject 310701 in study 20030213). The platelet count of this patient is listed in Table 12. This subject was positive for neutralizing antibodies to Romiplostim at week 79 (study discontinuation) and was negative for neutralizing antibodies to Romiplostim in a follow-up sample taken 4 months later. There is a severe thrombocytopenia following the discontinuation of Romiplostim for this patient. Neither sample from this patient was positive for binding antibodies to TPO and hence was not assessed for neutralizing antibodies against TPO.

Table 12. Platelet Count of the Patient with Positive Neutralizing Antibody to Romiplostim

Time	Baseline	Week 79	F/U 1-Month	F/U 2-Month	F/U 4-Month
Plt Counts (x 10^9/L)	31	37	7	20	12

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

None.

2.4.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

None.

2.4.3 Drug-Drug interactions

2.4.3.1 **Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?**

No.

2.4.3.2 **Is the drug a substrate of CYP enzymes?**

No.

2.4.3.3 **Is the drug an inhibitor and/or an inducer of CYP enzymes?**

No.

2.4.3.4 **Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

No.

2.4.3.5 **Are there other metabolic/transporter pathways that may be important?**

No studies on the metabolism of Romiplostim have been performed in humans or in animals. Metabolism studies are not generally performed for proteins which are degraded into amino acids that are then recycled into other proteins, small peptides and individual amino acid. Therefore classical biotransformation studies as performed for pharmaceuticals are not needed. No *in vitro* drug-drug interaction studies have been performed since P450 enzyme system is not expected to play any role in Romiplostim biotransformation.

2.4.3.6 **Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?**

No. Romiplostm is used as monotherapy.

2.4.3.7 **What other co-medications are likely to be administered to the target patient population?**

In the clinical trials, Romiplostim was used concomitantly with corticosteroids, danazol, azathioprine, IVIG, and anti-D immunoglobulin.

2.4.3.8 **Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

Romiplostim is proposed to be a monotherapy used to treat chronic ITP. No formal drug-drug interaction studies have been conducted for Romiplostim and concomitant medications.

2.4.3.9 **Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

None.

2.4.3.10 **Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?**

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative PK and PD?

The initial clinical manufacturing process, referred to as P1 for Romiplostim was used in support of phase 1, 2, and pivotal phase 3 clinical trials. The commercial drug substance manufacturing process, referred to as P2, [redacted] P2 [redacted] producing drug substance and drug product comparable to P1.

In Study 20030213, two subset studies were conducted to assess the PD comparability (Subset A) and PK comparability (Subset B) of the clinical process (P1) material and the commercial process (P2) material.

Study 20030213-Subset A (PD Comparability)

Twenty-two of 41 subjects who agreed to participate in Subset A were included in the analysis based on the following criteria. Subjects with ITP could participate in this subset if they had been receiving the P1 material in Study 20030213 for at least 20 weeks and they were expected to remain on study for at least 3 additional months after switching to the P2 material. All subjects in this subset were to be switched from the P1 material to the P2 material without changing the dose of Romiplostim. Individual dose adjustment was permitted after the first dose of P2 material. All subjects in Study 20030213 were permitted standard of care therapies including rescue medication if the investigator deemed necessary.

Mean platelet counts over 30 days pre-switch and 30 days post switch were 111.1 x 10^9/L

and 113.9 x 10^9/L for the P1 and P2 materials, respectively (Table 13). The mean difference in platelet counts in the 30-day periods before and after the switch was -2.8 x 10^9/L (P value =0.95) and the 90% confidence interval for the difference was -19.2 to 13.7 (Figure 14). This supports the comparability in the platelet response of these 2 materials.

Table 13. Comparison of Platelet Counts Over 30 Days Pre-Switch (for the P1 Material) and Post-Switch (for the P2 Material) in Subjects With ITP (Study 20030213-Subset A)

	Average Platelet Count[a] (x 10^9/L)		
	30-Day Pre-Switch (P1 Material)	30-Day Post-Switch (P2 Material)	Difference (Pre - Post)
N	22	22	22
Mean	111.13	113.91	-2.78
SD	76.19	82.28	44.85
Median	104.00	88.50	-8.70
Q1, Q3	45.40, 158.00	46.50, 165.25	-23.15, 10.67
Min, Max	14.4, 272.0	27.0, 322.5	-89.0, 99.0
90% Confidence Interval for Mean Difference			(-19.23, 13.68)

[a]For an individual subject, average platelet count is defined as the mean of available platelet counts within a 30-day period.
90% confidence interval of mean difference is based on paired t-test.

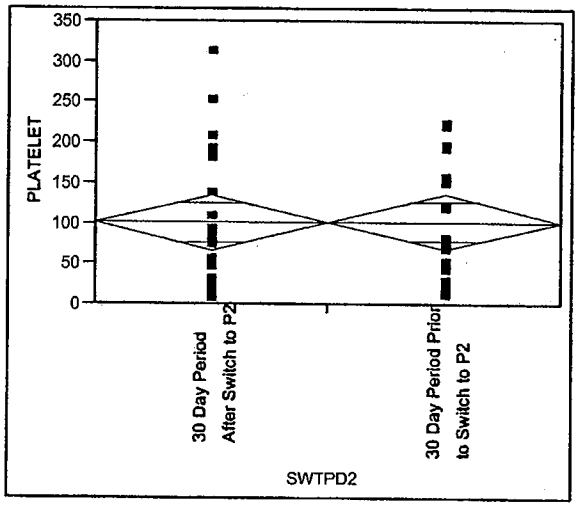


Figure 14. Platelet Counts over 30 days Pre-switch and 30 days Post switch (Study 20030213-Subset A)

Study 20030213-Subset B (PK Comparability)
Twenty subjects participated in this subset based on the following eligibility criteria: subjects with ITP who enrolled in Study 20030213 before the data cutoff date (28 November 2006), had received at least 3 consecutive doses of P2 material at 3 μg/kg or greater, were expected to be on study for at least 2 additional weeks, agreed to the serial blood draws, and were able to return to the investigational site 3 consecutive weeks for evaluations. For each individual subject, the same doses of Romiplostim using the P2 and P1 materials were administered in the following sequence: P2 material on week 1 (day 1) followed by P1 material on week 2 (day 8). A total of 19 PK samples were collected from each subject serially over 14 days; ie, for 7 days after P2 dose in week 1 and for 7 days after P1 dose in week 2. The platelet counts were measured at 3 time points: immediately before dosing of P2 material on week 1 (day 1), immediately before the dose of P1 material on week 2 (day 8), and at the end of the 7-day dosing interval on week 2 (day 15). The antibody sample was collected prior to the dose of P1 material.

Twenty subjects completed the treatment phase and received both the P1 and P2 materials. Data from 2 subjects were excluded from the comparability evaluation as follows: one due to a change in Romiplostim dose at the time of switch and the other due to sample mishandling during the study.

A mixed-effect model was used to analyze the data. In the model, material (P1 and P2) was treated as a fixed effect, subject as a random effect, and predose platelet count as a covariate. The AUC, C_{max}, and the predose platelet count were logarithmically transformed before the analysis. The mean exposure to Romiplostm (measured as AUC and C_{max}) from the P2 material relative to that from the P1 material and its 90% confidence interval were estimated. The probability associated with the difference in the mean AUC and C_{max} values between the P1 and P2 materials was also provided.
The mixed-effect model was represented by the following formula.

$$\log(AUC) = \text{subject} + b*\log(\text{predose platelet count}) + \text{material} + \varepsilon.$$
$$\log(C_{max}) = \text{subject} + b*\log(\text{predose platelet count}) + \text{material} + \varepsilon.$$

where b represents the effect of predose platelet counts, and ε represents the residual variability.

Results of the statistical analyses showed that the point estimate of the mean AUC ratio (P2 to P1) was 1.17 with the 90% confidence interval of 0.98 to 1.41, and the point estimate of the mean C_{max} ratio (P2 to P1) was 1.33 with the 90% confidence interval of 1.01 to 1.74 (Table 14).

Table 14. Comparison of AUC and C_{max} After SC Administration of P1 and P2 Materials (Study 20030213-Subset B)

	Mean Ratio (P2 to P1)		
Parameter	Point Estimate	90% Confidence Interval	p value
AUC	1.17	0.98, 1.41	0.11
C_{max}	1.33	1.01, 1.74	0.08

PK comparability data in subset B did not meet the standard bioequivalence criteria. These differences on the AUC and C_{max} may be due to the inadequate study design with multiple dose levels and small sample size andor real product difference.

2.5.1.1 **What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?**

An assessment of PD and PK comparability was done in an open-label extension study (Study 20030213). The PD comparability was established between P1 and P2 materials, but the PK comparability data did not meet the standard bioequivalence criteria. The differences in the $AUC_{0\text{-}7days}$ and C_{max} values may be contributed by the inadequate study design (multiple dose levels with small sample size at each dose level) and/or by the real product difference. The differences in PK observed between P1 and P2 materials did not result in clinical significant differences in platelet response. All patients in the phase 3 extension study have been switched to receive the P2 material with continuous collection of efficacy and safety data.

2.5.1.3 **If the formulations are not BE, what dosing recommendations should be made that would allow approval of the to-be-marketed formulation? (e.g., dosage adjustments may be made for injectables)**

Not applicable.

2.5.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable because Romiplostim is given via SC injection.

2.5.3 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Not applicable.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moiety identified and measured in the serum in the clinical pharmacology and biopharmaceutics studies?

Serum concentrations of Romiplostim were measured using a sensitive and specific enzyme-linked immunosorbent assay (ELISA), with a dynamic range of 18 to 500 pg/mL, and the LLOQ of 18 pg/mL. Assay methods and validation reports for Romiplostim assays in human serum are listed in Table 15.

Table 15. Analytical Methods and Validation for Quantification of Romiplostim in Human Serum

Assay Study No.	Capture Antibody	Secondary Antibody	Assay Range (pg/mL)	Study No.
101903			17.8-500	20000109 20000137 20040134
			18.6-500	20030105; 20030212 20030213 20030213-subset A
108854			15-1500	20030213-subset B

Assay 101903:

Assay validation consists of 5 accuracy and precision assays, assays for freeze-thaw analysis, bench top stability, dilutional linearity and long term stability.

The accuracy of the method was evaluated by comparing the measured values of the quality control samples in human serum with their respective nominal values at the following levels: QC1500.000 pg/mL, QC2 400.000 pg/mL QC3 250.000 pg/mL QC4 33.784 pg/mL and QC5 17.982 pg/mL.

- The % nominal values (AR) for the intra-spike QCs were 96% (QC1), 97% (QC2), 98% (QC3), 102% (QC4) and 97% (QC5).
- The intra-assay accuracy for the intra-spike QCs were 93-99% (QC1), 96-99% (QC2), 95-101% (QC3), 92-107%o (QC4) and 90-101% (QC5)
- The % nominal values (AR) for the inter-spike QCs were 94% (QC1), 94% (QC2), 97% (QC3), 97%(QC4) and 91% (QC5).

The precision is calculated in terms of the estimated standard deviation around the measured concentrations of the control samples, and is expressed as the percent coefficient of variation.

- The intra-assay, intra-spike, coefficient of variation (n=6) of the quality control samples ranged from 3-10% (QC1), 4-8% (QC2), 5-7% (QC3), 4-7%(QC4) and 6-8 % (QC5).

- The intra-assay, inter-spike, coefficient of variation (n=6) of the quality control samples ranged from 3-10% (QC1), 4-8% (QC2), 4-9% (QC3), 4-8% (QC4) and 6-11% (QC5).

Assay 108854:
The Validation of the Assay 108854 is listed in Table 16.

Table 16. Summary of Method Validation (Assay 108854) Inter-assay Accuarcy and Precision

Validation Parameter	Nominal Conc. (ng/mL)	Inter-assay Accuracy[a] (%RE)	Inter-assay Precision (%CV)	Total Error of Method[b] (%)	Precision of Duplicate Instrument Response[c] (%CV)
Standard Curve	15 to 1500	-3 to 8	2 to 8	NA	0 to 11
VS (H, M, L)	1100, 400, 40	-7 to 6	7 to 13	15 to 19	0 to 8
VS (LLOQ)	15	-4	21	26	0 to 17 (31*)
VS (ULOQ)	1500	3	8	11	0 to 4

[a]%RE: bias compared to nominal concentration
[b]Total Error = based on inter-assay accuracy and precision. The sum of Inter-assay accuracy (%RE: absolute value) + %inter-assay precision.
[c]%CV: minimum to maximum
* 31% CV happened only in one run as an outlier.

The quantification ELISA for the concentration of eTPO in serum had a range of 22 to 1000 pg/mL (Table 17).

Table 17. Analytical Methods and Validation Reports for Endogenous Thrombopoietin Concentration in Human Serum

Assay Study No. (Method No.)	Assay Range (pg/mL)	Assay Validated (Site)	Capture Antibody	Secondary Antibody	Amgen Study No.
101519 (0018)	22 – 500	Yes (Covance)	[redacted]		20000109
104031	31.25 – 1000	Yes (Amgen)	[redacted]		20030105 20030212 20050159

Validation of Assay 101519 is listed in Table 18.

Table 18. Analytical Methods and Validation for Endogenous Thrombopoietin Concentration in Human Serum

Performance Specifications

Dynamic Range	0.020-0.640 ng/mL
LLOQ	0.022 ng/mL
ULOQ	0.500 ng/mL

Accuracy and Precision

	Inter-Assay		Intra-Assay	
QC Concentration	Accuracy (%AR)	Precision (% CV)	Accuracy (%AR)	Precision (%CV)
0.022 ng/mL	86	7	83	5
0.025 ng/mL	93	6	95	4
0.030 ng/mL	99	4	100	4
0.050 ng/mL	97	3	97	3
0.100 ng/mL	99	6	99	8
0.500 ng/mL	99	4	98	4

2.6.2 Which metabolites have been selected for analysis and why?

There is no metabolite selected for analysis because Romiplostim is a protein.

2.6.3 For all moiety measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Not applicable because Romiplostim is a protein.

2.6.4 Antibody Measurements

In the initial phase of the ITP development program, the immunogenicity evaluation of the clinical studies was supported by a neutralization bioassay alone. The neutralization bioassay had sufficient sensitivity to allow an evaluation of the neutralizing antibody activity.

After the immunoassay was developed and validated, the immunogenicity evaluation followed a two-tiered approach.The first assessment employed a surface plasmon resonance-based screening immunoassay to detect and confirm the presence of binding antibodies to Romiplostim,and/or TPO in serum samples from study subjects. Any sample testing above the assay threshold required additional testing in a confirmatory specificity test. The second assay was a cell-based bioassay to detect neutralizing antibodies in vitro. All positive serum samples identified in the immunoassay were further evaluated in the cell-based bioassay for neutralizing antibody activity. Any sample meeting assay criteria required additional testing in a specificity test, and in a Protein G depletion test to further confirm that the specificity of the immune response was due to antibodies. The assay sensitivity and specificity for immunoassay and bioassay are listed in Table 17.

Table 17. Analytical Methods for Antibody Measurement

	Immunoassay		Bioassay	
	AMG 531	TPO	AMG 531	TPO
LOQ[a] (ng/mL)	400	200	400	200
Specificity	Depletion ≥ 50% with 6.4 µg/mL drug		-	
Drug Tolerance[b]	10 ng/mL	10 ng/mL	25 ng/mL	6.3 ng/mL

[a] LOQ (Limit of Quantitation) of an assay is the concentration of antibody that can be reliably detected above assay threshold.
[b] Drug Tolerance is defined as the maximum amount of drug that the assay can tolerate.
- not applicable

18 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Statistical- 1

APPENDICES

3.3 APPENDIX 1 - INDIVIDUAL STUDY REVIEWS

Clincia Pharmacology Sutdies

Study Number	Phase	Subjects	Material	Dose[a]; Schedule	Subjects Enrolled	Pharmacokinetics		Pharmacodynamics	
						Sampling Schedule[b]	Subject Number	Sampling Schedule[b]	Subject Number
20000109	1	Healthy	P1	0.3, 1.0, 10.0; SD (IV)[c] 0.1, 0.3, 1.0, 2.0; SD	48	Intensive	32	Intensive	48
20040134	1	Healthy, Japanese	P1	0.3, 1.0, 2.0, 3.0[c]; SD	30	Intensive	8	Intensive	30
20000137A	1/2	ITP	P1	0.2, 0.5, 1.0, 3.0, 6.0, 10.0; ≤ two doses	24	None	0	Intensive	24
20000137B	1/2	ITP	P1	1.0, 3.0, 6.0; QW	21	Intensive	17	Sparse	21
20010218	1/2	ITP	P1	30, 100, 300, 500[c]; ≤ two doses	16	None	0	Intensive	16
20050162	2	ITP, Japanese	P1	1.0, 3.0, 6.0; QW	12	None	0	Sparse	12
20030105	3	ITP, splenectomized	P1	1.0 to 15.0 (dose adjustment); QW	63	Sparse	18	Sparse	63
20030212	3	ITP, non-splenectomized	P1	1.0 to 15.0 (dose adjustment); QW	62	Sparse	10	Sparse	62
20030213	OLE	ITP	P1/P2	1.0 to 10.0[d] (dose adjustment); QW	137	Sparse	14	Sparse	137
Subset A					41[e]	Sparse	41[e]	Sparse	41[e]
Subset B					20	Intensive	20	Sparse	20

ITP = immune (idiopathic) thrombocytopenic purpura
OLE = Open label extension study enrolled subjects from any previous ITP studies conducted in the US/EU
SD = single dose: QW = every week
[a]The dose unit is µg/kg, except for µg unit dosing in Study 20010218; all doses were given by the SC route except for three cohorts in study 20000109 that had AMG531 given by the IV route
[b]Intensive samples were collected to provide PK or PD profiles; sparse samples were collected once weekly or less frequently
[c]The maximum planned doses of 3.0 µg/kg in Study 20040134 was not reached because stopping rules for excess elevation of platelet count were reached at the next lower planned dose.
[d]Subjects on previous studies could carry their doses forward into this study; the maximum dose across previous studies was 30 µg/kg. Subjects who were receiving a dose > 10 µg/kg prior to the amendment were allowed to remain on that dose; however, the subject's dose could not be further increased. If the subject's dose was decreased after enrollment, the dose could not be subsequently increased to > 10 µg/kg.
[e]22 of 41 subjects were qualified for inclusion in the analysis

In separate folder.

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3.4 APPENDIX 2 – PM REQUEST FORM

OFFICE OF CLINICAL PHARMACOLOGY

Pharmacometrics Consult Request Form

NDA or IND:	NDA	**App number:**	125268
Sponsor:	Amgen	**Brand Name:**	Nplate
Priority Classification:	P	**Generic Name:**	Romiplostim
Indication(s):	ITP	**Dosage Form:**	250 or 500 mg per 5 mL vial
Submission Date:	10/23/07	**Dosing Regimen:**	1 mcg/kg SC weekly
OCPB Review Due Date:	2/20/08	**Medical Division:**	DMIHP
PM Review Due Date:	2/15/08	**Reviewer:**	Angela Men
Advisory Meeting Date (if any):	Yes, March, 2008	**Team Leader:**	Hong Zhao
PDUFA / Action Date:	4/23/08		

Purpose of Pharmacometrics Request:	Review PM report regarding the PK/PD of Nplate

Appears This Way
On Original

3.5 APPENDIX 4 - OCP FILING REVIEW FORM

3.5.1 Office of Clinical Pharmacology

4 NDA/BLA FILING AND REVIEW FORM

4.1.1.1.1 General Information About the Submission

	Information		Information
BLA Number	125268	Brand Name	Nplate
OCP Division	5	Generic Name	Romiplostim
Medical Division	DHIMP/OODP	Drug Class	Analogous to endogenous thrombopoietin
OCP Reviewer	Angela Men	Indication(s)	ITP
OCP Team Leader	Hong Zhao	Dosage Form	250 or 500 mcg in one 5 mL vial
		Dosing Regimen	Initial dose 1 mcg/kg then once weekly
Date of Submission	10/23/07	Route of Administration	SC
Estimated Due Date of OCP Review	2/28/08	Sponsor	Amgen
PDUFA Due Date	4/23/08	Priority Classification	P
4.1.1.2 Division Due Date	3/17/08		

4.1.1.2.1.1.1.1 Clin. Pharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
4.2 HEALTHY VOLUNTEERS-				
single dose:	x	2		
multiple dose:				
4.2.1 Patients-				
single dose:				
multiple dose:	x	5		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	x	3		
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Comparability study	x	1		
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	x	10		

4.2.1.1.1.1 **Filability and QBR comments**		
4.2.1.2	"X" if yes	Comments
4.2.1.3 **Application filable?**	Yes	
4.2.1.4 **Comments sent to firm?**	**None**	
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA/BLAXXX, HFD-850(Electronic Entry or Lee), HFD-150(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125268/0 **Applicant: Amgen** **Submitted Date: 10/23/07**

Drug Name: Nplate (romiplostim) **BLA Type: Original** **Stamp Date: 10/23/07**

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the sponsor submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	√		
2	Has the sponsor provided metabolism and drug-drug interaction information?	√		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested at the earlier meeting (e.g.: Pre-NDA meeting), submitted in the appropriate format (e.g. CDISC)?	√		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		N/A	
	Studies and Analyses			
5	Has the Sponsor made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	√		
6	Did the sponsor follow the scientific advice provided regarding matters related to dose selection?	√		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	√		
8	Is there an adequate attempt by the sponsor to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		N/A	
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		N/A	
10	Did the sponsor submit all the pediatric exclusivity data, as described in the WR?		N/A	
11	Is the appropriate pharmacokinetic information submitted?	√		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR A NEW NDA/BLA

12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√		
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	√		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	√		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	√		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√		
17	Was the translation from another language important or needed for publication?		√	

Any Additional Comments: No additional Comments at this time.

Reviewing Pharmacologist — Date 11/14/07

Team Leader/Supervisor — Date 11/14/07

Office of Clinical Pharmacology
NDA/BLA Filing and Review Form

General Information About the Submission

	Information		Information
BLA Number	125268	Brand Name	Nplate
OCP Division	5	Generic Name	Romiplostim
Medical Division	DHIMP/OODP	Drug Class	Analogous to endogenous thrombopoietin
OCP Reviewer	Angela Men	Indication(s)	ITP
OCP Team Leader	Hong Zhao	Dosage Form	250 or 500 mcg in one 5 mL vial
		Dosing Regimen	Initial dose 1 mcg/kg then once weekly
Date of Submission	10/23/07	Route of Administration	SC
Estimated Due Date of OCP Review	2/28/08	Sponsor	Amgen
PDUFA Due Date	4/23/08	Priority Classification	P
Division Due Date	3/17/08		

Clin. Pharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
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HPK Summary	x			
Labeling	x			
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Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2		
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	5		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	2		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	x	3		
PK/PD:				
Phase 1 and/or 2, proof of concept:	x	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Comparability study	x	1		
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	x	10		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**Yes**	
Comments sent to firm?	**None**	
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		11/16/07
Secondary reviewer Signature and Date	Hoy Zhao	11/20/07

CC: NDA/BLAXXX, HFD-850(Electronic Entry or Lee), HFD-150(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)