

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125268

SUMMARY REVIEW

**DIVISION DIRECTOR'S
AND SUPPLEMENTAL CROSS DISCIPLINE TEAM LEADER REVIEW
MEMORANDUM**

BLA:	125268
DRUG:	Romiplostim
TRADENAME:	Nplate®
INDICATION:	"for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy."
FORMULATION:	250 and 500 mcg lyophilized product in single use vials to be reconstituted with sterile water for injection;
ROUTE:	Subcutaneous, administered only by health care providers
DOSE:	1 mcg/kg weekly _____, adjusted over subsequent weeks based on platelet count response to maximum of 10 mcg/kg
SPONSOR:	Amgen
SUBMITTED:	October 23, 2007
PDUFA DUE DATE:	July 23, 2008
DD MEMO COMPLETED:	June 9, 2008
DD MEMO PREPARERS:	Dwaine Rieves, MD, Director Division of Medical Imaging and Hematology Products Cross Discipline Team Leader for the Application
RECOMMENDED:	Approval

Dwaine Rieves 7-14-08

1. Introduction to Review:

Romiplostim is the first thrombopoietin product submitted to FDA for marketing consideration. This review follows the draft template proposed for cross discipline team leaders.

Romiplostim, a recombinant protein produced in E coli, is an Fc-peptide fusion protein that binds to the thrombopoietin (TPO) receptor on megakaryocytes (and other blood cells). Romiplostim binding to megakaryocytes results in platelet production in a manner that is thought to be similar to the action of endogenous TPO. However, Romiplostim has no amino acid sequence homology to endogenous TPO. Lack of this sequence homology may lessen the risk for immunogenicity; initial clinical studies of other recombinant TPO molecules (that did have sequence homology to endogenous TPO) resulted in antibody formation that caused thrombocytopenia in volunteers.

The Romiplostim clinical development program involved FDA discussions throughout the development process and included two confirmatory (phase 3) clinical studies to which FDA had provided SPA agreements. The confirmatory studies were thorough, especially considering the rarity of "relatively refractory" chronic ITP, and confirmed that the product increases functional platelet concentrations. The studies also identified several important safety risks which have been addressed in product labeling, a medication guide and a Risk Evaluation and Mitigation Strategy (REMS) that "restricts" distribution of the product to prescribers and patients enrolled in a special tracking program. This tracking program is focused upon detection of bone marrow fibrosis and other major safety risks as well as providing an assessment of the extent of any use of

the product among patients ~~_____~~ The assessment of "off label" use is especially important since a study of Romiplostim among patients with myelodysplasia syndrome (MDS) suggested that the product increases the risk for development of leukemia in these patients. This review will focus upon the clinical data and REMS.

Romiplostim had previously been designated as an "orphan drug product" by FDA.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status:

Romiplostim is the first member of the "class" of thrombopoietin products to be submitted for marketing authorization. Romiplostim is not currently marketed anywhere in the world.

3. CMC/Microbiology/Device:

The Romiplostim manufacturing data were reviewed by Dr. David Frucht (primary reviewer) and Dr. Kathleen Clouse (team leader). Both reviewers have determined that the manufacturing of the product is well controlled and leads to a product that is pure and potent and ready for approval. Indeed, all manufacturing concerns that arose during the review were resolved with no need for post-approval manufacturing commitments.

FDA reviewers performed inspections of the Drug Substance manufacturing and testing facilities in January, 2008 and these inspections disclosed no safety concerns.

4. Nonclinical Pharmacology/Toxicology:

Dr. Tushar Kokate was the primary reviewer of the animal data and Dr. Adebayo Laniyonu provided a secondary review of these data. Both reviewers recommended approval.

4.1. General nonclinical pharmacology/toxicology:

Definitive toxicology studies were performed in rats, Rhesus and Cynomolgus monkeys. In general, toxicity related to exaggeration of the expected thrombopoietin effects. Romiplostim is bioactive in these animal species (increases platelet counts) such that the animal data are very useful to estimating potential human toxicity. Most notably, the studies in rats indicated the development of myelofibrosis following prolonged Romiplostim exposure, a finding with clinical implications pertaining to a risk for marrow fibrosis. Animal data otherwise were notable for lack of evidence of potential QT prolongation effects.

4.2 Carcinogenicity:

The Romiplostim carcinogenic and mutagenic potential have not been evaluated in animals, consistent with the current guidance on biotechnology-derived pharmaceuticals. Clinical data have been obtained that address, in part, the carcinogenic potential.

4.3 Reproductive toxicology:

Reproductive toxicology studies were conducted in rats, rabbits and mice. Most notably, in studies of pregnant mice, Romiplostim at doses five times the maximum human dose, resulted in reduced maternal body weight and increased post-implantation embryo loss. In rats, at Romiplostim doses 11 times the maximum human dose, increased peri-natal pup mortality was observed. These findings are not unexpected since Romiplostim crossed the placenta "barrier" and studies have shown increases in fetal platelet counts.

As described in the product label, a registry is in place to track the results of pregnancies that occur among patients receiving Romiplostim. The label describes the pregnancy risks, as well as the need to temper these risks according to the clinical need for the drug.

4.4 Other Notable Nonclinical Issues:

No post-marketing nonclinical studies are necessary.

5. Clinical Pharmacology/Biopharmaceutics:

Dr. Angela Men was the primary pharmacology reviewer and a secondary review was performed by Dr. Hong Zhao. Both reviewers recommended approval.

5.1 General Clinical Pharmacology:

In vitro studies have suggested that Romiplostim clearance is likely dependent, in part, upon the concentration of TPO receptors within the body, especially TPO receptors on platelets and megakaryocytes. This expectation was supported by the major clinical pharmacology findings, which indicate more rapid clearance in patients with higher platelet counts.

Pharmacokinetics were studied in healthy subjects after intravenous Romiplostim and these data showed that clearance was dependent, in part, upon the platelet count. For example, subjects with higher platelet counts generally had lower blood Romiplostim concentrations than patients with lower platelet counts.

Pharmacokinetics were studied in patients, mainly in order to show that a change in the manufacturing process did not alter the product. In this study, prechange product was compared to postchange product and no important pharmacokinetic or pharmacodynamic alterations were observed.

Pharmacodynamic responses to Romiplostim are characterized by the platelet count response and are described within the clinical study data. In general, the platelet count response to Romiplostim increases as the Romiplostim dose increases.

5.2 Drug-drug Interactions:

No specific drug interaction studies were performed. However, patients in the clinical studies were receiving multiple concomitant medications and, given the nature of the product's mechanism of action, commonly used drugs (such as "cold medications") are not anticipated to alter the effects of Romiplostim.

5.3 Pathway of Elimination:

Romiplostim elimination has not been definitively determined although the available data (mainly *in vitro*) indicate that the protein is predominantly eliminated by binding to TPO receptors followed by internalization/degradation within the hematopoietic cell.

5.4 Special Population Considerations:

Geriatric: The clinical development program included 38 patients over the age of 65 years and 18 patients were over the age of 75 years. No differences in bioactivity or safety were evidenced, when older patients were compared to younger patients.

Pediatric: The application database did not include pediatric data. Amgen is currently performing a clinical study among pediatric patients with chronic ITP.

5.5 QT assessment:

A thorough QT study was not performed, consistent with the expectations for biologic products. QT effects were also not studied during the clinical development program. In general, the nature of the product's mechanism of action and the "relative refractory" nature of the patient population do not make QT assessment a priority for the product. Nevertheless, Amgen is including the performance of EKG/QT assessments within the planned subsequent studies of Romiplostim (including uses within patients with chemotherapy-induced thrombocytopenia).

5.6 Other Notable Clinical Pharmacology Issues:

The clinical pharmacologists emphasized the importance of post-marketing antibody formation assessments and the label includes directions for the prescriber to submit blood to Amgen for antibody assay, in situations of suspected immunogenicity (for example, decreases in platelet counts).

6. Clinical Microbiology:

Clinical microbiology was reviewed by the general chemistry review team and no unique concerns were identified.

7. Clinical/Statistical:

The clinical development program was conducted with general FDA and Amgen agreement on study design features. For example, FDA and Amgen agreed, *a priori* via SPA, that clinically important increases (and maintained) in platelet counts were appropriate primary endpoints for the confirmatory clinical studies, even without demonstrated benefits of reduction in hemorrhage. In general, this approach was regarded as reasonable given the clinical understanding of ITP pathophysiology and the logistical hurdles for using hemorrhage as a major study outcome.

The original BLA submission contained data from a total of:

- 9 studies of Romiplostim use among chronic ITP patients (exposure n = 204)
- 2 healthy subject studies (exposure n = 56)
- 1 chemotherapy-induced thrombocytopenia (lymphoma) interim study report (exposure n = 4)

-1 myelodysplasia-related thrombocytopenia interim study report (exposure n = 20)

These data were supplemented at the day 120 point in the review with additional interim information from the on-going clinical studies (mainly the extension study of ITP patients and the chemotherapy-induced thrombocytopenia studies). The final BLA database consisted of Romiplostim exposure to:

n = 271 patients with chronic ITP

n = 121 subjects/patients without chronic ITP

7.1.1 Dose Identification/selection and Limitation:

Overall, Amgen has studied Romiplostim among patients with chronic ITP as well as patients with chemotherapy-induced thrombocytopenia (CIT). Early clinical studies examined Romiplostim effects in healthy volunteers and these data were used to identify the dose for phase 3 ITP clinical studies. Pilot study data from patients with chronic ITP also supported the choice of Romiplostim dose for the phase 3 ITP clinical studies. The CIT clinical development program is on-going and very limited data (all available from phase 1 or 2 studies) were included within this BLA submission.

7.1.2 Phase 3 Clinical Studies

Two phase 3 clinical studies provide the main evidence of Romiplostim safety and efficacy and an "extension" study (open label/single arm) allowed long term/ongoing exposure to Romiplostim to patients who completed the phase 3 studies. The phase 3 studies were:

- a. Study 20030105 (referred subsequently as "study 105"): a study of patients who had undergone splenectomy
- b. Study 20030212 (referred subsequently as "study 212"): a study of patients who had not undergone splenectomy

Phase 3 Design features:

Except for the difference in "splenectomy status", the two phase 3 clinical studies used largely duplicate study designs with the major features outlined below:

-Eligibility: adults who had completed "at least one prior ITP treatment" and who had platelet counts of $\leq 30,000/\text{mcL}$

-Architecture: randomized (2:1 active: placebo), double-blind, 24 week treatment period followed by a 12 week period off study drug; randomization was stratified by use of any concomitant ITP medications (yes/no)

-Assessments: weekly platelet counts with regular laboratory/antibody/clinical evaluations; various patient reported outcomes were assessed regularly (SF36, ITP Questionnaire, etc)

-Dose: Romiplostim or placebo initially at 1 mcg/kg weekly with dose titration to maintain platelet counts between 50,000/mcL and 200,000/mcL; dose reduction

for platelet counts > 200,000/mcL and dose "hold" for platelet count > 400,000/mcL

-Primary endpoint: "Durable Platelet Response" defined as at least 6 weekly platelet counts \geq 50,000/mcL during the last 8 weeks of the study in the absence of use of "rescue medications" (i.e., no patient who needed "rescue medication" during the study could achieve the primary endpoint); the proportion of "responders" was compared between the two study groups (2 x 2 table/Cochran Mantel-Haenszel test stratified by baseline concurrent ITP therapy--yes/no)

-Secondary endpoints were to be summarized using descriptive statistics and consisted of various permutations of the platelet changes

Phase 3 Results:

a. Disposition and Baseline Characteristics: Overall, compliance with the study plans was acceptable with no notable imbalance in the numbers of subjects who discontinued (failed to complete) the studies. The sample sizes and distribution are shown in Table 1.

Table 1. Randomization and Distribution

Group	Study 105		Study 212	
	PI	Romi-	PI	Romi-
Randomized	21	42	21	41
Discontinued	2	2	4	2
Cause of Discontinuation				
Death	2	-	-	-
Adv Event	-	1	1	2
Pregnancy	-	-	1	-
Consent withdrawal	-	1	2	-

Major baseline characteristics are shown in Table 2. In addition to the shown characteristics, the subjects had generally completed multiple prior ITP medications (95% had completed steroids and 80% had received IVIG) and had low platelet counts despite these medications. Hence, the patient population was largely "refractory" to available therapies.

Table 2. Baseline Characteristics

Characteristic	Study 105		Study 212	
	PI n = 21	Romi- n = 42	PI n = 21	Romi- n = 41
Age, median	56	51	46	52
Female (%)	52	64	76	66
Plt ct, median, /mcL	14.7	13.5	19.3	18.7
Hgb, median, g/dL	14.5	13.7	12.5	13.6

b. Major Endpoint Results: Both studies showed large treatment effects, based upon the primary endpoint results, as shown in Table 3.

**Table 3. Primary Endpoint Results:
Proportion of Patients with a Durable Platelet Response**

Study	PI	Romi	p-value
105 (splenectomy)	0/21 (0%)	16/42 (38%)	< 0.01
212 (no splenectomy)	1/21 (5%)	25/41 (61%)	< 0.01

Major secondary endpoint results are summarized in Table 4 (where a platelet response is defined as a platelet count \geq 50,000/mcL). As shown here, less "rescue medication" was used among the Romiplostim group; the Romiplostim group also had more "overall platelet responses" (defined as patients with a durable response plus patients with a transient response—at least 4 weekly platelet responses), as well as many more weeks with any platelet response.

Table 4. Secondary Endpoint Results

Outcome	Study 105		Study 212	
	PI n = 21	Romi- n = 42	PI n = 21	Romi- n = 41
Overall Plt Response, n (%)	0	33 (79%)	3 (14%)	36 (88%)
Weeks with Plt Response, mean	0.2	12.3	1.3	15.2
Rescue Med use, n (%)	12 (57%)	11 (26%)	13 (62%)	7 (17%)
Durable Plt Resp & Stable Dose, n (%)	0	13 (31%)	0	21 (51%)

Overall, the phase 3 studies demonstrated a clinically and statistically persuasive increase in platelet counts that was maintained in a clinically meaningful manner. To further support the meaningfulness of the platelet increases, Amgen had performed a pilot clinical study that showed Romiplostim-stimulated platelets (in healthy volunteers) did not differ in function (aggregation studies) compared to non-stimulated platelets.

7.1.3 Other Efficacy Studies:

Pertinent to the phase 3 controlled clinical studies are the findings from the on-going extension study which showed that platelet counts were maintained in the majority of enrolled patients. Overall, within the entire ITP database, the median Romiplostim exposure was 37 weeks with 36 subjects exposed for two years.

7.1.4 Discussion of Primary and Secondary Reviewer's Comments and Conclusions:

The clinical reviewer situation with this BLA was complicated by FDA staff shortages and transitions. Shortly prior to submission of the BLA, the hematology team leader (Dr. Ruyi He) had a transfer and shortly prior to the mid-cycle, the primary reviewer (Dr. John Lee) had a transfer. Ultimately, the package consists of an interim review performed by Dr. Lee and a final primary review performed by Dr. Farank Jamali with assistance by Dr. Kassa Ayalew. All reviewers have recommended approval and have concerns predominantly related to the safe use of the product. All reviewers concur that the product provides clinically meaningful efficacy. Drs. Lee, Jamali and Ayalew importantly contributed to the development of the Risk Evaluation and Mitigation Strategy (REMS) as well as the post-marketing requirements/studies and label.

7.1.5 Differences in CDTL Reviewer and other Clinical Reviewer Conclusions:

In general, I concur with the major findings from the clinical reviews and I regard the reviewer conclusions as important contributions to the design of the post-marketing requirements/studies as well as labeling. As noted above, efficacy appears indisputable and safety concerns were relatively obvious to all reviewers.

7.1.6 Pediatric Use/PREA

Romiplostim has an "orphan drug" designation from FDA; hence, pediatric studies are not required under PREA. Nevertheless, Amgen is currently conducting study 20060195, a randomized, double-blind, placebo controlled, exploratory study in pediatric patients aged 1 to 17 years. In the study, 20 patients with chronic ITP are randomized to active drug or placebo (3:1 ratio) to receive treatment over at least 12 weeks; followed by eligibility for the on-going extension study.

7.1.7 Other Notable Efficacy Issues:

During the review period, some concern was expressed about the fact that the clinical database did not provide statistical evidence of decreased hemorrhage for Romiplostim-treated patients compared to patients in the placebo group. Given this concern the review team noted that the data indicated a "trend" toward decreased bleeding with Romiplostim and the Romiplostim background data pertaining to mechanism of action (stimulation of the TPO receptor in a manner very similar--if not identical--to that of endogenous TPO). Another consideration was the difficulty of quantifying "low grade" bleeding and the rarity of serious hemorrhage. Together, the review team members concluded that the evidence of a treatment effect (based mainly on platelet responses) is indisputable and reflects a clinically meaningful advantage in decreasing the risk for hemorrhage.

7.2 Safety:

7.2.1 General Safety Considerations:

Amgen performed placebo-controlled clinical studies of six months duration that provide important chronic ITP comparative information and the extension/single arm studies provide important supportive information. Another major source of safety information was the exploratory (dose-ranging--not placebo-controlled) study of Romiplostim among patients with MDS. This MDS study provided evidence that Romiplostim may increase the risk for MDS progression and/or leukemic transformation and strongly emphasized the need for relatively tight tracking of use of the drug in the post-marketing situation (especially given the prevalence of chemotherapy-induced thrombocytopenia, compared to ITP).

7.2.2 Safety Findings:

Overall, the safety database consisted of Romiplostim exposure in 271 patients with chronic ITP; exposure to 44 patients with MDS and 21 patients with CIT. The review disclosed five major safety concerns, as outlined below with basis for the concern.

1-potential for myelofibrosis with cytopenias

Background animal data indicated that Romiplostim induces myelofibrosis in rats. In the phase 3 controlled studies, one adverse event of "increased bone marrow reticulin" was observed in the Romiplostim group but no events were reported in the placebo group. The uncontrolled studies provide strong evidence of Romiplostim-induced increases in bone marrow reticulin (a potential precursor to collagen fibrosis). Specifically, nine patients in the uncontrolled studies had increased bone marrow reticulin observed after repetitive Romiplostim dosing and most of these patients had received "higher" Romiplostim doses (7 to 18 mcg/kg per week). Four patients who discontinued Romiplostim because of reticulin deposition had follow-up bone marrows. Two of the four patients had "improvement" in reticulin deposition after Romiplostim had been discontinued and two had "stable" reticulin in the marrow.

Together, the data indicate that Romiplostim causes reticulin fiber deposition in the bone marrow of some patients. This reticulin deposition may importantly signal a risk for collagen fibrosis/myelofibrosis with cytopenias.

2-Severe thrombocytopenia after Romiplostim discontinuation:

The available data signal a safety concern for hemorrhage due to severe thrombocytopenia after Romiplostim discontinuation (ie., thrombocytopenia of even greater severity than at baseline). One of the theoretical risks for use of a thrombopoietin product is suppression of any endogenous TPO such that profound, severe thrombocytopenia might result following discontinuation of the thrombopoietin product. The main clinical evidence for this risk comes from the phase 1 and 2 studies (n = 57 patients receiving Romiplostim) where four subjects experienced severe thrombocytopenia (platelet counts even lower than at baseline) following discontinuation of Romiplostim. The severe thrombocytopenia was not associated with important bleeding and platelet counts returned to baseline levels by 14 days after Romiplostim discontinuation.

3-Thrombotic events:

A hypothetical risk for Romiplostim relates to the occurrence of thromboses as a consequence of excessive increases in platelet counts. Only three patients experienced thrombotic events in the controlled clinical study (one in placebo group; two in Romiplostim group) while 12 patients experienced thromboses in the uncontrolled clinical studies. The thrombotic events were not consistently related to excessive platelet counts. Close attention to Romiplostim dose adjustment should minimize the risk for thromboses.

4-Antibody formation:

Conceivably, antibodies may form to Romiplostim that cross react/neutralize endogenous TPO, thereby causing severe thrombocytopenia. In the clinical development program, no neutralizing antibodies to TPO were detected among the 225 tested ITP patients and one patient developed neutralizing antibodies to Romiplostim (this patient's antibodies were detected following Romiplostim discontinuation). "Binding" antibodies (of unclear significance) to Romiplostim or TPO were detected among 10% and 5%, respectively, of the tested population.

Antibody formation continues in ongoing clinical studies and product labeling describes the risk and management procedures for suspected antibody development.

5-Neoplasia:

Since Romiplostim binds to the TPO receptor on hematopoietic cells and stimulation of this receptor has been implicated in leukemia/lymphoma development/progression, one of the hypothetical risks for Romiplostim is neoplasia development or worsening. In the controlled studies, neoplasia events occurred in 5 patients in the placebo group and 2 patients in the Romiplostim group. However, in a single arm clinical study of 44 patients with MDS (as updated during the review), 11 patients were reported as having disease progression, among whom four patients had confirmed acute myelogenous leukemia. Multiple patients had blast cells detected in the peripheral blood that prompted discontinuation of Romiplostim. These data, while not conclusive, provide important evidence of a potential risk for hematologic neoplasia among patients who are at risk for the neoplasia, such as patients with MDS.

7.2.3 Safety Update:

The safety update provided supplemental information from the on-going studies and did not reveal safety concerns that were not evident in the original submission.

7.2.4 Immunogenicity:

Covered above. No patients have been shown to develop neutralizing antibody formation to TPO in the clinical development program.

7.2.5 Special Safety Concerns:

The five items listed above form the major safety concerns and importantly influenced labeling and development of a REMS.

7.2.6 Discussion of Primary Reviewer's Comments and Conclusions:

The reviewers were consistent in general recommendations and conclusions.

7.2.7 Notable Safety Issues:

As noted above, five topics represent important safety issues to be addressed with the labeling and REMS.

8.0 Advisory Committee:

Romiplostim was discussed at a March 12, 2008 Oncologic Drugs Advisory Committee and the committee unanimously regarded the safety and efficacy data as persuasive of a favorable risk:benefit.

9. Other Relevant Regulatory Issues: PMR and REMS

The most notable regulatory issue relates to the post-marketing requirements and REMS.

Post-marketing Requirements:

- a. To conduct study 20080009, "A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)." In this trial, at least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule will apply to the detection of antibody formation to Romiplostim and thrombopoietin as well as the electrocardiographic (ECG) detection of cardiac conduction abnormalities. Final report is due by _____ 2014.
- b. To conduct an "Antibody Registry Study" that will enroll subjects who have received Romiplostim and whose blood samples contain antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack or loss of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers are to submit blood samples to Amgen for detection of antibodies to romiplostim and thrombopoietin. The Antibody Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.
- c. To conduct an observational pregnancy study/registry.
- d. To conduct a "milk only" lactation study/registry.

Major Features of the REMS:

- a. Medication guide
- b. FDA-approved communication plan to include specific text for healthcare provider materials and institutional materials. The education process (as well as prescriber certification/patient registry) is referred to as the "HCP NEXUS" program (Network of Experts Understanding and Supporting Nplate and Patients)
- c. Elements to assure safe use: drug distribution is limited to prescribers and patients who enroll in the NEXUS program.

-all prescribers must be "certified" by Amgen; certification involves signing a specific document (prescriber enrollment form) that attests to familiarity with the labeling and agreement to comply with the expectations of the NEXUS program/patient registry.

-To comply with the registry/program, prescribers must:

- sign and submit the "healthcare provider enrollment form"
- at enrollment of a patient, complete a "patient enrollment form" and "patient baseline data form."

- obtain signature of each patient to confirm participation in the NEXUS program/disclosure of information to the program
- complete a form every six months to verify that continued treatment is appropriate and to actively solicit (yes/no--check list) major safety outcomes using a "Safety Questionnaire."
- complete a "patient discontinuation" form if Nplate is discontinued; a post-discontinuation form must also be completed six months later (six months after drug discontinuation).

Note:

_____ The REMS assessments are to be performed frequently for the first two years following product launch and regularly thereafter.

10. Financial Disclosure:

The BLA contained the expected extent of financial disclosure by study investigators. No deficiencies were identified.

11. Labeling:

The labeling was completed, to include a Medication Guide, with extensive input from the review team, the Office of Surveillance and Epidemiology and multiple consultants.

12. DSI audits:

The DSI performed an audit of four clinical sites for the phase 3 clinical studies. No major deficiencies were identified and the clinical data were assessed as having no evidence of important deficiencies in data integrity.

13. Conclusions and Recommendations:

I and all BLA review disciplines recommend approval of Romiplostim with the agreed-upon labeling and risk management program. The clinical development program provided persuasive evidence of safety and efficacy and, most notably, was sufficiently extensive to identify a number of important risks for long term use of the product. These risks will be addressed through the risk management plan and the required post-marketing studies.