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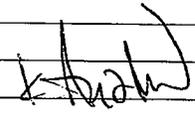
APPLICATION NUMBER:

BLA 125268

CROSS DISCIPLINE TEAM LEADER REVIEW

CDU 125268/0
Kassa Ayalew, M.D.,
STN 125268/0
Platelet Receptor
Acting Team Leader

Cross-Discipline Team Leader Review

Date	Tuesday, May 20, 2008
From	Kassa Ayalew, M.D., Acting Team Leader 
Subject	Clinical Team Leader Review
BLA #	STN 125268/0
Proprietary / Established (USAN) names	Nplate /Romiplostim
Dosage forms / strength	SC injection QW/250 mcg (5mL vial), 500 mcg (5mL vial)
Proposed Indication(s)	Treatment of Thrombocytopenia in Chronic Immune (Idiopathic) Thrombocytopenic Purpura (ITP)
Recommended:	Approval

1. Introduction to Review

On October 23, 2007, Amgen, Inc. submitted a new orphan biologic license application (STN 1251660) to the Division of Medical Imaging and Hematology Products (DMIHP) for Nplate Romiplostim. The submission was for the use of Nplate (Romiplostim) for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura who are refractory to low-dose corticosteroids or splenectomy.

The clinical team recommends approval of this BLA on the basis of the two controlled phase 3 studies and one open label extension study submitted for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura who are refractory to low-dose corticosteroids or splenectomy.

Nplate is an Fc fusion protein produced by recombinant DNA technology in Escherichia coli, stimulates platelet production by binding to the thrombopoietin receptor. Nplate increases platelet production through binding and activation of the TPO receptor(c-Mpl), a mechanism analogous to endogenous TPO. The elimination of serum Nplate 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. The peak serum concentrations of Nplate is about 7 to 50 hours post-dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days).

For this BLA, David Frucht provides the chemistry review, Dr. Tushar Kokate Provides the pharmacology/toxicology review, Dr. Angela Men provides the clinical pharmacology review, Dr. Yuan W Chen provides the statistical review and Dr. Jamali Faranak provides the clinical review, Dr. Suzanne Berkman provides the review form Office of Surveillance and Epidemiology perspective, Dr. Richardae Araojo provides the review from Maternal and Pediatric Health perspective and Mr. Richard Abate, provides Division of Medication Errors and Technical Support (DMETS) review.

2018-01-10
Kavita Agrawal
STW 1251
H. J. Kim
For Treatment of T1

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

The material reviewed in this BLA was derived from the clinical studies conducted by the Applicant, and the review was based on the data from the two controlled phase 3 studies and an open label extension study.

Nplate has received orphan designation for this proposed indication in major global regions, United States (US) (2003),

3. CMC/Microbiology/Device

The CMC review was completed by Dr. David M. Frucht who recommends approval. There are no CMC related Phase 4 commitments.

Review of Microbiology/ Device was not applicable.

4. Nonclinical Pharmacology/Toxicology

According to Dr. Tushar Kokate review, the non clinical studies are sufficient to support the approval of this BLA. There are no outstanding non clinical issues.

5. Clinical Pharmacology/Biopharmaceutics

Dr Angela Yuxin Men was the clinical pharmacology reviewer for this BLA. Her recommendations for Phase 4 commitments are as follows:

- To conduct a long-term clinical study on immunogenicity that assesses the impact of antibodies to Nplate (Romiplostim) and/or to thrombopoietin (TPO) on the efficacy and safety of Nplate (Romiplostim).
- 
- To assess the potential of Nplate (Romiplostim) treatment on QT interval following the principles described in the ICH E14 guidance (<http://www.fda.gov/cber/gdlms/iche14qtc.pdf>).

6. Clinical Microbiology

N/A.

7. Clinical/Statistical

Dr. John Lee a medical reviewer in the Division of Medical imaging and Hematology Products performed part of the clinical review of the submission. This clinical review recapitulated the findings by Dr. John Lee and updated the safety and efficacy data.

Dr. Faranak Jamali who completed the clinical review and recommends approval for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adults who are refractory to low-dose corticosteroids or splenectomy.

Dr. Yuan Who Chen a statistical review. Dr. Yuan W Chen recommends approval.

7.1. Efficacy

Please see section 7.1.2

7.1.1. Dose identification/selection and limitations

In the two phase 3 clinical trials, the study drug was administered subcutaneously (SC) once per week at a starting dose of 1 $\mu\text{g}/\text{kg}$. Dose adjustment was allowed throughout the 24-week treatment period to allow subjects to maintain platelet counts in the target range of 50 to 200 $\times 10^9/\text{L}$. The maximum permitted dose was 15 $\mu\text{g}/\text{kg}$.

After 24 weeks of treatment, investigational product was withdrawn and the platelet count monitored. Participation was complete once platelet counts were $\leq 50 \times 10^9/\text{L}$ or the subject reached week 36 with a platelet count $> 50 \times 10^9/\text{L}$, whichever occurred first. Subjects in both arms were eligible to receive rescue medication throughout the study. Rescue medication was permitted for bleeding or wet purpura, or if the subject was at immediate risk of bleeding. Concurrent ITP therapies could be reduced during the first 12 weeks of treatment once platelet counts were $> 100 \times 10^9/\text{L}$. Pre-dose sampling for pharmacokinetic (PK) studies were performed once the patient reached a dose of $\geq 10 \mu\text{g}/\text{kg}/\text{week}$.

7.1.2. Phase 3 clinical studies

The applicant submitted the two phase 3 and an open label extension studies to support the regulatory decision. The studies are the following:

- (1) Study 20030212 (study 1, non- splenectomized) conducted in patients who have not yet undergone splenectomy, enrolled 21 patients receiving placebo and 41 patients receiving Nplate.
- (2) Study 20030105 (study 2, splenectomized), conducted in patients status post splenectomy, enrolled 21 patients receiving placebo versus 42 patients receiving Nplate.

- (3) Study 20030213 (study 3, extension study), uncontrolled, open-label extension study, conducted in patients who have completed an earlier Nplate study, provided clinical experience supporting the continued safety and effectiveness of Nplate with long-term use. Patients in the extension study included 100 patients who completed one of the pivotal studies, either in the treatment or the placebo arm.

A total of 125 patients were included in the two phase 3 studies (divided almost equally). Both studies were multicenter, double-blind, placebo controlled and patients were randomized (2:1; active: placebo). The study patients had at least one prior ITP medication prior to enrollment.

Except for the splenectomy status, the two studies had largely the same inclusion criteria and design features. The baseline characteristics of enrolled ITP patients were similar between the placebo and Nplate arms, with most subjects having received multiple prior ITP medications. In both studies the pretreatment platelet count was $\leq 30 \times 10^3/\mu\text{L}$ (mean of 3 counts during screening).

The study drug was administered subcutaneously (SC) once per week at a starting dose of 1 $\mu\text{g}/\text{kg}$. Dose adjustment was allowed throughout the 24-week treatment period to allow subjects to maintain platelet counts in the target range of 50 to 200 $\times 10^9/\text{L}$. The maximum permitted dose was 15 $\mu\text{g}/\text{kg}$. After 24 weeks of treatment, investigational product was withdrawn and the platelet count monitored. Participation was complete once platelet counts were $\leq 50 \times 10^9/\text{L}$ or the subject reached week 36 with a platelet count $> 50 \times 10^9/\text{L}$, whichever occurred first.

Subjects in both arms were eligible to receive rescue medication throughout the study. Rescue medication was permitted for bleeding or wet purpura, or if the subject was at immediate risk of bleeding. Concurrent ITP therapies could be reduced during the first 12 weeks of treatment once platelet counts were $> 100 \times 10^9/\text{L}$. Pre-dose sampling for pharmacokinetic (PK) studies were performed once the patient reached a dose of $\geq 10 \mu\text{g}/\text{kg}/\text{week}$.

The primary endpoint in both studies was "durable platelet response," defined as at least six weekly platelet counts $\geq 50,000/\text{mcL}$ during the last eight weeks of study drug treatment, in the absence of "rescue medications" at any time during the 24 week treatment period. The major secondary endpoints involved comparisons of platelet count "responses" (defined as any weekly platelet count $\geq 50,000/\text{mcL}$) and the use of thrombocytopenia "rescue medications." Patients were exposed to the study drug for 24 weeks with weekly platelet count measurements followed by 12 weeks of observation with out the study drug administration. Patients who had completed Study 1 and 2 and whose platelet counts subsequently decreased to $\leq 50 \times 10^9/\text{L}$ were allowed to receive Nplate in an open-label extension study with weekly dosing based on platelet counts.

Results

A total of 125 male and female subjects, 18 months to ≥ 65 years of age, were randomized to receive Nplate or placebo. All patients had been treated and failed current first-line therapies for ITP (94% patients had received corticosteroids 80% had received IVIG). Of the 125 patients who began the studies, 115 (92%) subjects (85.7% placebo and 95.2% Nplate) completed the study.

The median age of enrolled patients in the study was 52 years. Female to male ratio is almost 2:1 in both arms, as expected in ITP. Majority of patients were Caucasians (82%), 9(7.2%) were Black and 5 (4%) were Asians. There were no clinical important differences in the baseline demographic characteristics including the baseline median platelet [$16-18 \times 10^3/\mu\text{L}$] And endogenous thrombopoietin between the two treatments. Compared to non-splenectomized patients, patients who were splenectomized had slightly lower median platelet counts.

The, efficacy endpoints were analyzed based on the full analysis set that consisted of all randomized subjects. Safety endpoints were analyzed using the safety analysis set defined as all randomized subjects who received at least one dose of Nplate. The statistical tests were to be two sided at $\alpha = 0.05$.

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In both studies, statistically significant differences were observed for the primary endpoint and secondary endpoints, as shown in the Table below:

Table 1: Primary and Secondary Endpoint Results

Outcome	Study 1 (non- splenectomized patients)		Study 2 (splenectomized patients)		p-value*
	Placebo n = 21	Nplate n = 41	Placebo n = 21	Nplate n = 42	
Secondary endpoints					
Durable platelet response	1(5%)	25(61%)	0 (0%)	16 (38%)	< 0.01
Secondary endpoints					
Overall platelet response	3 (14%)	36 (88%)	0 (0%)	33 (79%)	< 0.01
Weeks with platelet response, mean (SD)	1.3 (3.5)	15.2 (7.5)	0.2 (0.5)	12.3 (7.9)	< 0.01
Subjects requiring rescue medication	13 (62%)	7 (17%)	12 (57%)	11(26%)	< 0.01
Subjects with durable platelet response with "stable dose"	0 (0%)	21 (51%)	0 (0%)	13 (31%)	< 0.01

*p-value was similar for each study; "stable dose" was defined as a dose maintained within ± 1 mcg/kg during the last 8 weeks of treatment.

Nplate was effective in achieving a durable platelet response in patients with ITP, irrespective of splenectomy status, and the effectiveness appears to be greater in patients with less severe disease (splenectomy not required for adequate management) than in patients with more severe disease (splenectomy performed to manage refractory disease).

A significantly greater proportion of patients in the Nplate group achieved the secondary endpoints (overall platelet response, number of weeks with platelet counts $\geq 50 \times 10^9/L$) and less number of patients in the Nplate group required rescue therapy. The results were consistent with those for the primary endpoint.

In addition, numerically greater number of patients (27.4% vs. 7%) in Nplate group had > 25% dose reduction in concurrent therapy and discontinuation of baseline therapy for ITP (14.3% vs. 7.1 %) when compared to patients received placebo.

Despite the achievement in the durable platelet response and secondary endpoints, the incidence of bleeding events during treatment, regardless of grade and cause, was 61 % in the placebo group and 57% for Nplate. The observed difference in any serious bleed between Nplate and placebo group was also numerically small. (See the table below)

Table 2: Incidence rate of bleeding adverse events in the phase 3 controlled studies

Adverse event	Placebo n = 41	Nplate n = 84
Any bleed	25 (61%)	48 (57%)
Any serious bleed	4 (10%)	5 (6%)

Hundred patients from the two controlled phase 3 trials were subsequently entered to the ongoing, multicenter, open-label, and extension study of Nplate. The primary endpoint of this study was to evaluate the safety of Nplate as a long-term treatment in thrombocytopenic subjects with immune (idiopathic) thrombocytopenic purpura (ITP). The secondary endpoints are incidence of platelet response (platelet response is defined as a doubling of baseline platelet count and platelet count $\geq 50 \times 10^9/L$ in the absence of rescue Medication) within the preceding 8 weeks and reduction in the dose or discontinuation of concurrent ITP therapies while receiving Nplate. The efficacy results obtained from the uncontrolled long-term extension study were consistent with those obtained from the controlled pivotal studies. However, the uncontrolled experience suggests that efficacy of Nplate may decline over time with prolonged use. The use of rescue medication did not differ appreciably among patients in the extension study, irrespective of treatment status (Nplate vs. placebo) in previous controlled studies.

7.1.3. Other efficacy studies

There were no other efficacy studies.

7.1.4. Discussion of primary and secondary reviewers' comments and conclusions

The primary clinical reviewer Dr. Faranak Jamali recommends approval of Nplate for treatment of adult patients with ITP who are refractory to low-dose corticosteroids or splenectomy.

7.1.5. Pediatric use/PREA waivers/deferrals

This is an orphan indication PREA does not apply.

7.1.6. Discussion of notable efficacy issues

Nplate has demonstrated clinical and statistical significant achievement in durable platelet response in patients with ITP, irrespective of splenectomy status. Nplate effectiveness was greater in patients with less severe disease (splenectomy not required for adequate

management) than in patients with more severe disease (splenectomy performed to manage refractory disease).

No drug has demonstrated such kind of results to date.

7.2. Safety

7.2.1. General safety considerations

The safety population included 271 patients with chronic ITP who received at least one dose of Nplate. The data submitted was adequate for review.

The demographic characteristics of patients exposed to Nplate was similar to those observed in the two phase 3 controlled studies.

The median duration of exposure in the two phase 3 placebo-controlled studies was 24 weeks (mean weekly dose 3.30 ($\mu\text{g}/\text{kg}/\text{week}$). However, patients in the safety database were exposed to Nplate for approximately 37 weeks. (4.4 $\mu\text{g}/\text{kg}/\text{week}$).

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7.2.2.Safety findings from submitted clinical trials – general discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.

In the safety findings identified in the two phase randomized clinical study are presented below.

Table 3: Overall Summary of Adverse Events in Controlled Phase 3 Studies

	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)
Subjects Reporting Any Adverse Events	39 (95.1)	84 (100.0)
Subjects Reporting Adverse Events with Severity of		
Severe	12 (29.3)	23 (27.4)
Life-threatening	1 (2.4)	4 (4.8)
Fatal	3 (7.3)	1 (1.2)
Subjects Reporting Any Serious Adverse Events	8 (19.5)	14 (16.7)
Subjects Reporting Any Treatment-Related Adverse Events	11 (26.8)	34 (40.5)
Subjects Reporting Treatment-Related Adverse Events with Severity of		
Severe	0 (0.0)	8 (9.5)
Life-threatening	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Subjects Reporting Any Treatment-Related Serious Adverse Events	0 (0.0)	2 (2.4)
Subjects Who Withdrew from Study Due to Adverse Events	1 (2.4)	3 (3.6)

Source: Sponsors Submission

Both groups reported similar rate of severe and serious adverse events. The number of subjects reporting life threatening adverse events was numerically higher in Nplate arm.

The study duration-adjusted event rate (events/100 subject-years on study) for fatal adverse events for the entire ITP study population (n=271) was less than placebo-treated subjects in the controlled studies (8 (2.9%) vs. 3 (7.3%)).

Overall Deaths

Overall Summary of fatal Adverse Events in ITP population studied (phase 3 studies & Total number of ITP patients exposed to Nplate) is summarized below:

Table 4: Fatal Adverse Events

	Phase 3 Controlled Trials		Total Number of ITP Patients Exposed to Nplate
	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)	(N = 271) n (%)
Number of Subjects Reporting Fatal Adverse Events	3(7.0)	1(1.2)	8(3.0)
Pneumonia atypical	1(2.4)	0	0
Pulmonary embolism	1(2.4)	0	0
Cerebral hemorrhage	1(2.4)	1(1.2)	1(0.4)
Pneumonia pneumococcal	0	0	1(0.4)
Cardiac arrest	0	0	1(0.4)
Renal failure	0	0	1(0.4)
Aplastic anemia	0	0	1(0.4)
Thrombophlebitis	0	0	1(0.4)
Intestinal infarction	0	0	1(0.4)
Acute respiratory distress syndrome	0	0	1(0.4)

The number of patients experiencing fatal adverse events during the phase 3 controlled studies was numerically higher in the placebo group. Although, the incidence of fatal adverse events appears to increase with long term exposure, the rate remains below the placebo group.

The only death occurred in 80-year-old white man, randomized to Nplate, with a past medical history of congestive heart failure, hypertension, rectal cancer, partial colectomy, and venous stasis. His baseline platelet count was $9 \times 10^9/L$. The subject received weekly injections of Nplate over approximately 5 months at doses ranging between 1-3 $\mu g/kg$; with corresponding platelet counts ranging between 9 to $167 \times 10^9/L$. Three days after the last (21st) injection of Nplate at 3 $\mu g/kg$, patient was hospitalized for serious, life-threatening, right-sided cerebrovascular accident. 7 days later, patient developed a serious intracranial hemorrhage, a drop in platelet count $5 \times 10^9/L$ and died.

Discontinuations

The rate of adverse events leading to dropouts and/or discontinuations was higher in the Nplate group than the placebo group. The 3 patients in Nplate arm who dropped out/discontinued include a case of B cell lymphoma involving the bone marrow, a patient with worsening of bone marrow reticulin fibrosis, and a case of death due to intracranial hemorrhage.

The incidence of Dropouts and/or Discontinuations in the controlled phase 3 studies is summarized in the table below:

Table 5: Incidence of Dropouts and/or Discontinuations

	Placebo N=41 n (%)	Nplate N=84 n (%)
Total n of patients	1 (2.4%)	3 (3.6%)
B cell lymphoma	0	1 (1.2%)
Intracranial hemorrhage	0	1 (1.2%)
Bone marrow disorder	0	1 (1.2%)
Metastasis to liver	1(2.4%)	0

With the small number of SAEs (not more than 1 in 84) in the controlled studies, making a conclusion about the association with the drug is difficult.

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General Adverse Events

In the placebo-controlled studies, a greater proportion of patients on Nplate reported headache, fatigue, epistaxis, arthralgia, contusion, diarrhea, upper respiratory tract infection, dizziness, insomnia, myalgia, back pain, nausea, pain in extremity, abdominal pain, injection site bruising (and pain), oral mucosal blistering, pain, pharyngolaryngeal pain, shoulder pain, aesthenia, peripheral edema, hematoma, pyrexia, dyspepsia, anemia, and paresthesia.

Evaluation of the rest of common adverse events suggests very little numerical difference in the incidence and severity of adverse events between Nplate and placebo. The common adverse events are summarized in the Table below:

Table 6: Incidence of Adverse Events \geq 5% Nplate or Placebo Group by Preferred Term

Preferred Term	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)
Headache	13 (31.7)	29 (34.5)
Fatigue	12 (29.3)	28 (33.3)
Epistaxis	10 (24.4)	27 (32.1)
Arthralgia	8 (19.5)	22 (26.2)
Contusion	10 (24.4)	21 (25.0)
Petechiae	9 (22.0)	14 (16.7)
Diarrhoea	6 (14.6)	14 (16.7)
URI	5 (12.2)	14 (16.7)
Dizziness	0 (0)	14 (16.7)
Insomnia	3 (7.3)	13 (15.5)
Myalgia	1 (2.4)	12 (14.3)
Back Pain	4 (9.8)	11 (13.1)
Nausea	4 (9.8)	11 (13.1)
Pain in Extremity	2 (4.9)	11 (13.1)
Cough	7 (17.1)	10 (11.9)
Anxiety	5 (12.2)	9 (10.7)
Gingival Bleeding	5 (12.2)	9 (10.7)
Abdominal Pain	0 (0)	9 (10.7)
Muscle Spasms	4 (9.8)	8 (9.5)
Injection Site Bruising	2 (4.9)	8 (9.5)
Nasopharyngitis	7 (17.1)	7 (8.3)
Oral Mucosal Blistering	3 (7.3)	7 (8.3)
Pain	3 (7.3)	7 (8.3)
Pharyngolaryngeal Pain	2 (4.9)	7 (8.3)
Shoulder Pain	0 (0)	7 (8.3)

Ecchymosis	6 (14.6)	6 (7.1)
Asthenia	2 (4.9)	6 (7.1)
Edema Peripheral	2 (4.9)	6 (7.1)
Haematoma	1 (2.4)	6 (7.1)
Pyrexia	1 (2.4)	6 (7.1)
Dyspepsia	0 (0)	6 (7.1)
Rash	4 (9.8)	5 (6.0)
Anemia	1 (2.4)	5 (6.0)
Injection Site Pain	1 (2.4)	5 (6.0)
Paraesthesia	0 (0)	5 (6.0)
Vomiting	3 (7.3)	4 (4.8)
Chest Discomfort	3 (7.3)	3 (3.6)
Urinary Tract Infection	3 (7.3)	3 (3.6)
Injection Site Haematoma	3 (7.3)	1 (1.2)
Toothache	3 (7.3)	1 (1.2)

Source: Sponsors Submission

Laboratory Findings

There were no major clinically significant differences in the incidence of laboratory findings between Nplate and placebo groups.

7.2.3. Safety update

The 120 day safety update has been incorporated in this review.

7.2.4. Immunogenicity, where pertinent

There was only one patient who developed neutralizing antibodies against Nplate (1/225 among ITP subjects tested (1/225 or 0.44%). The impact of antibody development on the efficacy and safety of Nplate is currently unknown.

Therefore, it is recommended to evaluate the incidence of developing binding and neutralizing antibodies to Nplate and/or to the endogenous thrombopoietin (eTPO) and assess the clinical significance of antibody development on the efficacy and safety of Nplate in the long-term.

7.2.5. Special safety concerns

The following table summarizes the incidence of adverse events of special interest in patients exposed to Nplate.

Table 7: Incidence of the adverse events of special interest in patients exposed to Nplate compared to placebo.

	Phase 3 controlled studies		Total Number of ITP Patients Exposed to Nplate N=271
	Placebo N=42	Nplate N=84	
Number of Thrombotic / Thromboembolic Events	1 (2.4%)	2 (2.4%)	15 (5.5%)
Number of Bone Marrow Abnormality Events/Reticulin Deposition	0 (0.0%)	1 (1.2%)	10 (3.7%)
Number of Neoplasms	5 (12.0%)	2 (2.4%)	20 (7.3%)

The incidence of thrombotic/thromboembolic adverse events, bone marrow abnormalities and Number of Neoplasms was numerically higher in Nplate treated ITP patients. The incidence rates of the above events increased with long term exposure.

A difference in the incidence rate of the above adverse events between phase 3 controlled studies and comprehensive ITP safety set may be observed due to a difference in exposure parameters and/or other variables that were unaccounted in the uncontrolled studies. Therefore generalization is not possible.

The 10 patients with bone marrow abnormality events (reticulin deposition) have received Nplate doses ≥ 5 mcg/kg and six had received doses ≥ 10 mcg/kg. Progression to marrow fibrosis with cytopenias was not reported in the controlled clinical studies.

7.2.6. Discussion of primary reviewer’s comments and conclusions

There was no difference or disagreement between CDTL and primary review team. I concur with the primary reviewers’ conclusion.

7.2.7. Pre-Approval Safety Conference (If an NME that will be approved) (If a Post marketing Safety Conference was not held, explain why).

A Pre-Approval Safety Conference was conducted. The findings of the safety review were discussed and are included in this review and in Dr Faranak Jamali’s review of safety.

7.2.8. Discussion of notable safety issues

Please see section 7.2

8. Advisory Committee Meeting

The results of the above studies were reviewed by the agency and presented to Advisory Committee on March 12, 2008. At that time, the AC unanimously voted in favor of the adequacy of the data to support the safety and efficacy of Nplate.

9. Other Relevant Regulatory Issues

None.

10. Financial Disclosure

Financial disclosure information was submitted to the BLA. There was no evidence of financial conflict of interest.

11. Labeling

Labeling has been completed.

11.1. Proprietary name

The proprietary name Romiplostim was found acceptable.

11.2. Physician labeling

The final revision for the Nplate (Romiplostim) physician labeling was found acceptable.

11.3 Carton and immediate container labels

Ms Richard Abate's review, Division of Medication Error Prevention recommends that the applicant revise the carton and container labels using one color in the presentation of the proprietary name.

11.4 Patient labeling/Medication guide

This is subcutaneous (SQ) formulation that ~~is subcutaneous (SQ) formulation that~~. The revised Patient Labeling/ Medication Guide were found

acceptable. Ms. Richard Abate's review, Division of Medication Error Prevention recommends that the applicant revise the carton and container labels using one color in the presentation of the proprietary name.

12. DSI Audits

Ms. Karen Storm's review, Division of Scientific Investigations, indicates that the quality and integrity of the submission were acceptable. Four sites were inspected regarding the two controlled phase 3 trials and the extension study. With the limited information provided for four sites, no major deficiencies were noted that could compromise the integrity of the data.

13. Conclusions and Recommendations

All disciplines recommend approval of Nplate for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adults who are refractory to low-dose corticosteroids or splenectomy.

In the reviewed studies, Nplate demonstrated substantial evidence of effectiveness in raising the platelet counts in chronic ITP patients who have insufficient response to corticosteroids, immunoglobulins or splenectomy. The adverse event profile of Nplate was acceptable.

As noted by Dr Faranak Jamali, Nplate administration may also increase the risk for development or progression of reticulin fiber deposition, thromboembolic events, post-cessation thrombocytopenia, neoplasm and the risk for immunogenicity. Therefore, it is recommended that the sponsor continue to proactively monitor long-term safety and efficacy (including bone marrow fibrosis, thromboembolic events, post-cessation thrombocytopenia, and immunogenicity) and develop comprehensive dosing strategy to optimize product safety. It is also recommended that the sponsor completes a formal QT cardiac safety study, conducts lactation study and implement pregnancy exposure registry.

13.1. Recommended regulatory action

All review team members recommend approval.

The CDTL recommendation for this application is also approval. The recommendation is based on a review of safety and efficacy information on adult patients with ITP who are refractory to low-dose corticosteroids or splenectomy treated with Nplate.

13.2. Safety concerns to be followed postmarketing

As noted in Dr Faranak Jamali's review, the following five major safety concerns should be addressed through postmarketing studies. The safety concerns are:

- (1) reticulin formation and risk for marrow fibrosis
- (2) risk for malignancy or progression of malignancy
- (3) thromboembolic events
- (4) alteration of intrinsic TPO/worsening of thrombocytopenia after cessation of Nplate(Romiplostim) therapy
- (5) immunogenicity

13.3. Risk Minimization Action Plan

As noted in Dr Suzanne Berkman's review, it is recommended that the sponsor perform the REMS (risk evaluation and mitigation strategy) to optimize the appropriate use of Nplate to treat adult patients with chronic ITP, improve understanding of the risk profile of Nplate by monitoring for and assessing the serious adverse events associated with the identified and potential risks. The REMS should include education of patients and physicians about the risk profile of Nplate and appropriate use of this drug, limit off-label use in patients with other thrombocytopenic states, monitor, track, and assess identified and potential safety risks of Nplate in all patients with chronic ITP who will be receiving Nplate.

13.4. Postmarketing studies, voluntary or required

The following postmarketing studies (PMC) are recommended to the sponsor. Please see the action letter for the finalized PMC's.

1. 
2. 
3. To collect blood samples in patients with chronic ITP who receive long term Nplate treatment to test the incidence of binding and neutralizing antibodies to Nplate and/or to the endogenous thrombopoietin (TPO). The impact of the appearance of these antibodies on clinical efficacy and safety should be assessed. Please submit your proposed study plan and the time frame.
4. To develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women

exposed to Nplate during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, reticulatin formation, thrombotic events, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, please review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fml.htm>.

5. To conduct a milk only lactation study in a subset of women enrolled in the Nplate pregnancy registry, who choose to breastfeed their infants. This study should be designed to detect the presence and concentration of Nplate in breast milk and any effects on milk production and composition. The study should include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Changes are currently being made to the Draft Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling <http://www.fda.gov/cder/guidance/5918dft.pdf>. The Maternal Health Team can answer questions surrounding current thinking on protocol design.

Postmarketing Study Commitments subject to reporting requirements of 21 CFR 601.70.

6.  
7. 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)
8. 

13.5. Comments to be conveyed to the applicant in the regulatory action letter

Please see the action letter