

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**BLA 125268**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**BLA/Serial Number:** BB 125268/0

**Drug Name:** Nplate (Romiplostim)

**Indication(s):** Idiopathic Thrombocytopenic Purpura

**Applicant:** Amgen

**Date(s):** Date submitted: October 23, 2007  
PDUFA due date: April 23, 2007  
Review completion date: February 10, 2007

**Review Priority:** Priority

**Biometrics Division:** CDER/OB/DBV

**Statistical Reviewer:** Yuan Who Chen, Ph.D.

**Concurring Reviewers:** Jyoti Zalkikar, Ph.D.  
Aloka Chakravarty, Ph.D.

**Medical Division:** HFD-160 (DMIHP)

**Clinical Team:** Faranak Jamali, M.D.  
Kathy Robie-Suh, M.D.  
Rafel Rieves, M.D.

**Project Manager:** Florence Moore

**Keywords:** Idiopathic Thrombocytopenic Purpura, romiplostim, endogenous thrombopoietin, eTPO, platelet, splenectomy, ITP, placebo-controlled, double-blind

# Table of Contents

<b>1. EXECUTIVE SUMMARY .....</b>	<b>3</b>
1.1 CONCLUSIONS AND RECOMMENDATIONS .....	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES .....	3
1.3 STATISTICAL ISSUES AND FINDINGS .....	4
<b>2. INTRODUCTION .....</b>	<b>6</b>
2.1 OVERVIEW .....	6
2.2 DATA SOURCES .....	6
<b>3. STATISTICAL EVALUATION.....</b>	<b>7</b>
3.1 EVALUATION OF EFFICACY.....	7
3.2 EVALUATION OF SAFETY .....	14
<b>4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS .....</b>	<b>14</b>
4.1 GENDER, RACE AND AGE .....	14
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS.....	14
<b>5. SUMMARY AND CONCLUSIONS .....</b>	<b>15</b>
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE .....	15
5.2 CONCLUSIONS AND RECOMMENDATIONS .....	17
<b>SIGNATURES/DISTRIBUTION LIST PAGE (OPTIONAL).....</b>	<b>18</b>

## 1. EXECUTIVE SUMMARY

BLA 125268/0 is the original submission by Amgen for Nplate (romiplostim). The indication sought by the applicant is the treatment of patients with idiopathic thrombocytopenic purpura. The efficacy results obtained from two Phase III pivotal studies were included in the submission as documents for Agency review.

### 1.1 Conclusions and Recommendations

Based upon the efficacy results presented by the sponsor and this reviewer's statistical evaluation of the two pivotal studies, the applicant has provided sufficient evidence of efficacy of Nplate in the treatment of patients with chronic idiopathic thrombocytopenic purpura (ITP). One of the two pivotal studies enrolled subjects who were non-splenectomized and had an inadequate response to corticosteroids and/or immunoglobulins. The other study enrolled subjects who were splenectomized and had an inadequate response to splenectomy. The efficacy results from the two pivotal studies support the indication claim.

### 1.2 Brief Overview of Clinical Studies

Studies 20030105 and 20030212 were the two Phase III pivotal clinical trials included in the submission. Those were randomized, double blind, placebo-controlled studies using Nplate administered subcutaneous (SC) injection once per week in the treatment of patients with ITP. The study designs for the two studies were exactly the same; except 20030105 enrolled splenectomized subjects and 20030212 enrolled non-splenectomized subjects. A total of 63 and 62 subjects were randomized to either placebo or Nplate group in a ratio of 1:2 in Studies 20030105 and 20030212, respectively.

All patients received 24 weeks of treatment. The starting dose was 1 µg/kg and dose adjustment was allowed during the 24 week treatment period in order to maintain platelet counts in the range of 50 to 200 x 10<sup>9</sup>/L. The maximum dose was 15 µg/kg. Reductions in concurrent ITP therapies could occur during the first 12 weeks of treatment once a subject counts were > 100 x 10<sup>9</sup>/L. After 24 week treatment period, participation either withdrew from the follow-up phase once platelet counts ≤ 50 x 10<sup>9</sup>/L or reached Week 36 with a platelet count > 50 x 10<sup>9</sup>/L. Subjects in both arms were eligible to receive rescue medication throughout the duration of the study.

The primary objective of the two studies was to evaluate the efficacy and safety of Nplate in the treatment of thrombocytopenia in subjects with ITP. The primary endpoint was the incidence of durable platelet response. The durable platelet response was defined as achieving at least 6 weekly platelet responses during the last 8 weeks of treatment without any rescue medication. A weekly platelet response was defined as a platelet count of ≥ 50 x 10<sup>9</sup>/L on the weekly scheduled dose day. The secondary efficacy endpoints included incidence of overall platelet response, number of weeks with platelet response, proportion of subjects requiring rescue medications, and incidence of achieving durable platelet response with stable dose.

The study period of 20030105 was from March 29, 2005 to September 5, 2006, and 20030212 initiated on April 4, 2005 with ending on December 21, 2006.

### 1.3 Statistical Issues and Findings

1. The majority of subjects in both pivotal studies were recruited from the sites in the United States (77.8% and 87.1%, respectively). Table 1 presents the durable platelet response rates for those US subjects only, by study and treatment group. The treatment efficacy that measured by durable platelet response was retained for the subjects only recruited from the US sites only.

Table 1 Durable Platelet Response for US Subgroup, by Study

Study	Placebo	NPlate	p-value
20030105 US subjects	0.0% (0/17)	34.4% (11/32)	0.006
20030212 US subjects	5.9% (1/16)	59.5% (22/37)	0.0002

In addition, primary efficacy analysis by gender subgroup and Caucasian subjects also presented similar efficacy results. Tables 12 and 13 in Section 4.1 show the details (see page 15).

2. Subject 3651 of Study 20030212, a Hispanic female with age of 26 from Site 036, was randomized to placebo group. This subject received 3 doses of Nplate at weeks 19, 22 and 24. The following SAS output in Table 2 shows that her platelet counts were boosted after receiving Nplate treatment. In sponsor's analysis, this subject was counted as a placebo subject with no durable platelet response. With the worst scenario, this reviewer performed Cochran-Mantel-Haenszel test adjusted for the status of baseline ITP therapy with treating Subject 3651 as a placebo durable platelet responder. The test result demonstrated the Nplate treatment efficacy was robust ( $p < 0.001$ ).

Table 2 Platelet Counts from Week 18 to Week 25 for Subject 3651

ID	Week	Platelet	Site	Group
3651	Week 18		036	Placebo
3651	Week 19		036	Placebo
3651	Week 20		036	Placebo
3651	Week 21		036	Placebo
3651	Week 22		036	Placebo
3651	Week 23V2		036	Placebo
3651	Week 24V1		036	Placebo
3651	Week 24V2		036	Placebo
3651	Week 25		036	Placebo

3. In Study 20030105, only 2 placebo subjects (9.5%) discontinued study, whereas 2 subjects (Subjects 1231 and 1630) (4.8%) in the Nplate arm discontinued study. One placebo subject and 2 Nplate subjects discontinued study prior to week 18. Both of the two Nplate subjects were not durable platelet responders.

In Study 20030212, four placebo subjects (19.0%) discontinued study, whereas 2 subjects (Subjects 419 and 6050) (4.9%) in the Nplate arm discontinued study. Three placebo subject and 1 Nplate subjects discontinued study prior to Week 18 (8 weeks before the end of 24 weeks treatment). Both of the two Nplate subjects were not durable platelet responders.

Based on the protocol, if no platelet measurements were available on the weekly scheduled dose day, then that week was considered to have had no platelet response. Since only a few subjects did not complete study in both two pivotal trials and none of those Nplate subjects with missing data were identified as durable platelet responders, missing data had little impact on the primary efficacy analysis results.

4. Studies 20030105 and 20030212 had very similar study design. In order to investigate the timing of treatment effect and any potential factors that might contribute to platelet response, the data from Nplate treated subjects of the two studies were pooled. Table 3 shows the distribution of time to the first weekly platelet response. Subjects were categorized as durable platelet response group, transient platelet response group, and non-responder. Those subjects who were not durable platelet responders nor transient platelet responders were defined as the non-responders. The transient platelet responders were those who were not durable platelet responders but had at least 4 weekly platelet response during the last 8 treatment weeks.

It can be found in Table 3 that 85% of subjects in the durable platelet response group had their first weekly platelet response prior to Week 5. In contrast, 86% of non-responders did not have the first weekly platelet response prior to Week 5. In section of Evaluation of Safety (see page 13), tables of distribution of time to first platelet increase  $\geq 20,000/\mu\text{L}$  (Table 7) and distribution of number of weekly platelet response (Table 8) present information consistent with the information in Table 3.

Table 3 Distribution of Time to First weekly Platelet Response

Time of First Weekly Platelet Response	Durable Platelet Response Group N=41	Transient Platelet Response Group N=28	Non-Responder N=14
1 <sup>st</sup> Week	15 (36.6%)	9 (32.1%)	1 (7.1%)
2 <sup>nd</sup> Week	12 (29.3%)	3 (10.7%)	0 (0.0%)
3 <sup>rd</sup> Week	5 (12.2%)	10 (35.7%)	1 (7.1%)
4 <sup>th</sup> Week	3 (7.3%)	1 (3.6%)	0 (0.0%)
5 <sup>th</sup> Week or Later	6 (14.6%)	5 (17.8%)	12 (85.8%)

In order to identify the factors that could have impact on the non-responsiveness, logistic regression analysis was performed by this reviewer. Non-responder vs. durable/transient response was the outcome variable in the logistic regression model. Number of previous ITP therapy, time to first weekly platelet response and status of splenectomy were input variables, adjusted for age and gender. Time to first weekly platelet response was dichotomized with the cutoff of 4<sup>th</sup> week and 5<sup>th</sup> week plus.

Results showed that number of previous ITP therapy and time to first weekly platelet response were statistically significant in the logistic regression model. The variable of status of splenectomy is also important for future studies.

In summary, sponsor's data showed that splenectomy patients receiving more previous ITP therapies prior to Nplate treatment and having no weekly platelet response during the first 4 weeks of Nplate treatment are more likely to become a non-responder to Nplate treatment.

## 2. INTRODUCTION

### 2.1 Overview

Immune (idiopathic) thrombocytopenic purpura is an autoimmune disorder that is usually characterized by platelet destruction caused by antiplatelet autoantibodies. A substantial proportion of these patients have lower than expected concentrations of endogenous TPO (eTPO) for thrombocytopenic patients and normal and/or reduced platelet production.

Nplate is a recombinant protein that is expressed in E Coli. Nplate stimulates platelet production by a mechanism similar to that of eTPO. Initial studies in subjects with ITP suggested that Nplate increased platelet counts in thrombocytopenic patients with ITP regardless of splenectomy status or concurrent ITP medication use.

Study 20030105 was a randomized, placebo-controlled, Phase III study in patients with ITP who were refractory to splenectomy. Study 200302121 had a similar study design but enrolled subjects who had not undergone splenectomy.

All patients received 24 weeks of either placebo or Nplate treatment. The starting dose was 1 µg/kg and the maximum dose was 15 µg/kg. Dose adjustment was allowed during the 24 week treatment period in order to maintain platelet counts in the range of 50 to 200 x 10<sup>9</sup>/L. Reductions in concurrent ITP therapies could occur during the first 12 weeks of treatment once a subject counts were > 100 x 10<sup>9</sup>/L. The algorithm was defined as: 2 µg/kg/week if the platelet count was 10x10<sup>9</sup>/L or less and 2 µg/kg/2-week if the platelet count was between 11x10<sup>9</sup>/L and to 50x10<sup>9</sup>/L. In maintenance period, dose was increased by 1 µg/kg every week if 10x10<sup>9</sup>/L or less; increased by 1 µg/kg after 2 weeks if between 11x10<sup>9</sup>/L and to 50x10<sup>9</sup>/L; reduced by 1 µg/kg after 2 consecutive weeks at 201x10<sup>9</sup>/L to 400x10<sup>9</sup>/L. Subjects in both arms were eligible to receive rescue medication throughout the duration of the study.

## 2.2 Data Sources

The sponsor provided data electronically. All of the data can be located through the path of \\Cbsap58\M\CTD\_Submissions\STN125268\125268.enx. All variables of the datasets that included in the submission were well-defined and documented. SAS codes that used to generate tables and analysis results were also included in the submission.

## 3. STATISTICAL EVALUATION

This report includes the detailed statistical review of the pivotal studies 20030105 and 20030212.

### 3.1 Evaluation of Efficacy

#### 3.1.1 Primary Efficacy Endpoints

The primary endpoint was the incidence of durable platelet response. The durable platelet response was defined as achieving at least 6 weekly platelet responses during the last 8 weeks of treatment without any rescue medication. A weekly platelet response was defined as a platelet count of  $\geq 50 \times 10^9/L$  on the weekly scheduled dose day.

**Missing Data Imputation:** If no platelet measurements were available on the weekly scheduled dose day, then that week was considered to have had no platelet response. Subjects who discontinued early from the study were not considered to have had a weekly platelet response after study discontinuation. For secondary efficacy endpoints, any weekly platelet response achieved before the administration of rescue medication or study discontinuation was counted as a platelet response.

**Determination of sample size:** Assuming of achieving durable platelet response with placebo and Nplate was 10% and 50%, respectively, the sample size of 60 subjects with a 1:2 randomization ratio (Placebo: 20 subjects and Nplate: 40 subjects) would have 87% statistical power to detect the difference using a 2-sided Fisher's exact test at a significance level of 0.05.

**Randomization:** All the patients were randomly assigned into either placebo or Nplate group in a ratio of 1:2. The randomization was stratified by the concurrent ITP therapy (yes/no).

No interim analyses were planned or conducted.

**3.1.2 Secondary Efficacy Endpoints** included: Incidence of overall platelet response, number of weeks with platelet response, proportion of subjects requiring rescue medications, and incidence of achieving durable platelet response with stable dose (dose maintained within  $\pm 1 \mu\text{g}/\text{kg}$  during the last 8 weeks of treatment). Overall platelet response was defined as durable platelet response or transient platelet response. The transient platelet response

was defined as having at least 4 weekly platelet response during the 24 treatment weeks but not satisfying the criteria for durable platelet response.

### 3.1.3 Patient Disposition, Demographic and Baseline Characteristics

**Patient Disposition:** In Study 20030105, a total of 63 subjects were randomized to either placebo (N=21) or Nplate group (N=42). All of those randomized subjects received at least one dose of investigational drug. Only 4 subjects (placebo: 2, Nplate: 2) terminated early in the study.

Similarly, in Study 20030212, a total of 62 subjects (placebo: N=21 and Nplate: N=41) were randomized and all of the 62 subjects received at least one dose of investigational drug. Only 6 subjects terminated early in the study (Placebo: 4 and Nplate: 2).

All of the subjects who did not complete study in both trials were not durable platelet responders. Table 4 summarizes the patient disposition for both studies.

Table 4 Patient Disposition, by Treatment Group and by Study

	Study 20030105		Study 20030212	
	Placebo	Nplate	Placebo	Nplate
<b>Randomized</b>	21	42	21	41
<b>Received Treatment</b>	21	42	21	41
<b>Completed Study</b>	19	40	17	39
<b>Discontinued Study</b>	2	2	4	2
<b>Discontinued Study Prior to Week 18</b>	1	2	3	1
<b>Discontinued Study During Weeks 18-24</b>	1	0	1	1

#### **Demographic and Other Baseline Characteristics:**

Demographics and baseline characteristics (full analysis set) are summarized in Table 5 for placebo and Nplate group by study.

Males and females had similar distributions in placebo and Nplate groups in both two studies. The majority of patients was Caucasians (81.6%) and recruited from the US sites (82.4%). There were no statistically significant between group differences for the status of baseline concurrent ITP therapy in both studies. There were no statistical between group differences in mean age for both studies.

Table 5 Demographics and Baseline Characteristics, by Study

	Study 20030105		Study 20030212	
	Placebo	Nplate	Placebo	Nplate
<b>Overall</b>	<b>21 (100.0%)</b>	<b>42 (100.0%)</b>	<b>21 (100.0%)</b>	<b>41 (100.0%)</b>
<b>Gender</b>				
Female	11 (52.4%)	27 (64.3%)	16 (76.2%)	27 (65.9%)
Male	10 (47.6%)	15 (35.7%)	5 (23.8%)	14 (34.1%)
<b>Ethnicity</b>				
Caucasian	19 (90.5%)	34 (81.0%)	18 (85.7%)	31 (75.6%)
Others	2 (9.5%)	9 (19.0%)	3 (14.3%)	10 (24.4%)
<b>Country</b>				
US	17 (81.0%)	32 (76.2%)	17 (81.0%)	37 (90.2%)
Non-US	4 (19.0%)	11 (23.8%)	4 (19.0%)	4 (9.8%)
<b>Age (years)</b>				
Mean $\pm$ SD	53.9 $\pm$ 13.4	51.1 $\pm$ 15.6	55.0 $\pm$ 21.7	53.3 $\pm$ 15.5
Median	56.0	50.5	46.0	52.0
Range	(26, 72)	(27, 88)	(23, 88)	(21, 80)
<b>Years since ITP diagnosis</b>				
Mean $\pm$ SD	11.0 $\pm$ 8.8	12.8 $\pm$ 12.4	4.1 $\pm$ 5.2	4.1 $\pm$ 5.7
Median	8.5	7.8	1.6	2.2
Range	(1.1, 31.4)	(0.6, 44.8)	(0.1, 16.2)	(0.1, 31.6)
<b>Time since splenectomy</b>				
< 6 months	0 (0.0%)	7 (16.7%)	N/A	N/A
$\geq$ 6 months	21 (100.0%)	35 (83.3%)		
<b>Concurrent ITP therapy</b>				
Yes	7 (33.3%)	14 (33.3%)	8 (38.1%)	16 (39.0%)
No	14 (66.7%)	28 (66.7%)	13 (61.9%)	25 (61.0%)

### 3.1.4 Statistical Methodologies

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 investigational products. All statistical tests were to be two-sided at  $\alpha = 0.05$ .

**Primary Efficacy Analysis:** The primary efficacy endpoint was the incidence of durable platelet response, i.e. achieving at least 6 weekly platelet responses during the last 8 weeks of treatment from Weeks 18 to 24. Subjects who received rescue medications at any time during the treatment period were not considered to have had durable platelet response.

The Cochran-Mantel-Haenszel test was used to compare the durable platelet response rates between placebo and Nplate group with adjusting for the status of concurrent ITP therapy at baseline. Exact 95% confidence intervals for the incidence of durable platelet response were calculated, and normal approximations were used for the difference between the two groups.

**Secondary Efficacy Analyses:** The incidence of overall platelet response, proportion of subjects requiring rescue medications, and incidence of durable platelet response with stable dose were analyzed using the Cochran-Mantel-Haenszel test with adjusting for the status of concurrent ITP therapy at baseline. The number of weeks with platelet response during Weeks 2 to 25 between groups was compared using the analysis of variance with treatment, status of baseline ITP therapy as the input variables in the model.

**Analysis of Safety Data:** Safety was assessed by examination of treatment-emergent adverse events, clinical laboratory results, ECG data, and vital sign measurements collected during the treatment phase and post-treatment phase.

*Appears This Way  
On Original*

### 3.1.5 Results and Conclusions

**Primary Efficacy Results:** 38.1% and 61.0% Nplate subjects were identified as durable platelet responders in Studies 20030105 and 20030212, respectively. Compared to placebo subjects (0.0% and 4.8%, respectively), results from both two pivotal studies showed significant effect using Nplate in the treatment of patients with ITP ( $p=0.0013$  and  $p<0.0001$ , respectively). Table 6 shows the durable platelet response rates and corresponding 95% confidence intervals for placebo and Nplate group in each study.

**Table 6 Primary Efficacy Results: Comparison of Durable Platelet Response Rate between Treatment Groups, by Study**

	Study 20030105		
	Placebo (N=21)	Nplate (N=42)	p-value
Durable platelet response Incidence rate (%) 95% CI	0.0% (0/21) (0.0%, 16.1%)	38.1% (16/42) (23.6%, 54.4%)	0.0013
	Study 20030212		
	Placebo (N=21)	Nplate (N=41)	p-value
Durable platelet response Incidence rate (%) 95% CI	4.8% (1/21) (0.1%, 23.8%)	61.0% (25/41) (44.5%, 75.8%)	<0.0001

Figures 1 and 2 show the percentages of subjects with weekly platelet response in the two studies, respectively. It is easy to see in the two figures that approximately 50% or more Nplate subjects had weekly platelet response after Week 4 and continuously reserved the pattern until Week 25. It appears that Nplate subjects in Study 20030212 who were non-splenectomy patients had numerically higher percentage of subjects with weekly platelet response at later stage of treatment period than those in Study 20030105 who were splenectomy patients.

Figure 1 Percentage of Subjects with Weekly Platelet Response (20030105)

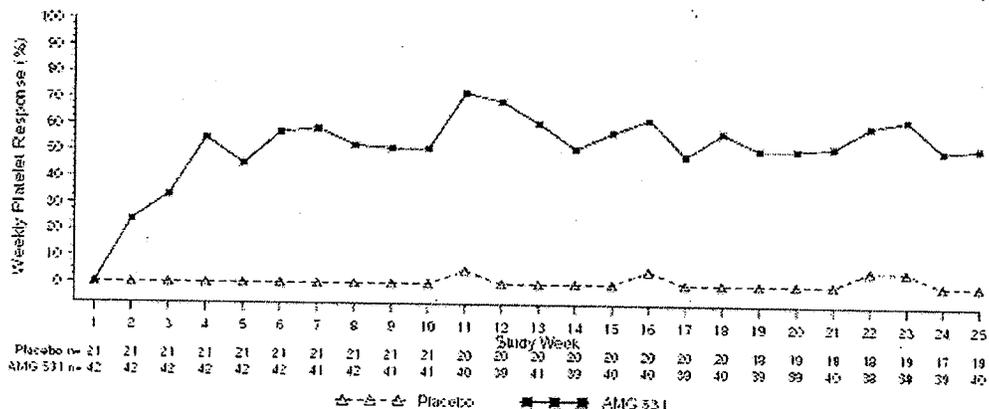
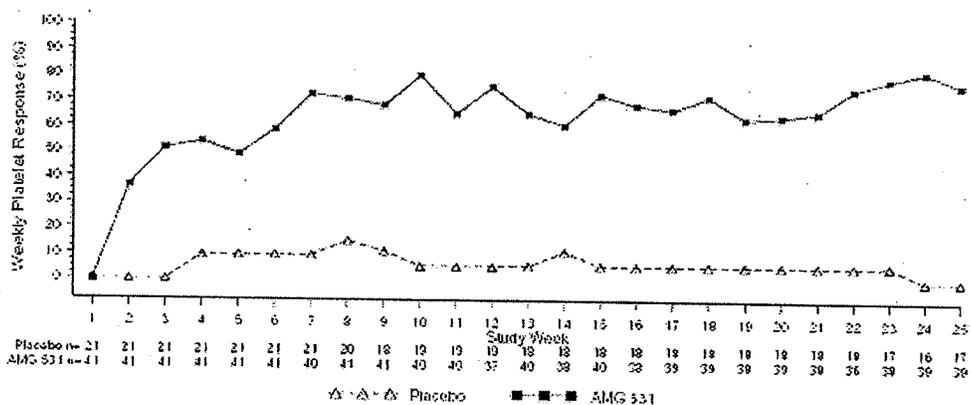


Figure 2 Percentage of Subjects with Weekly Platelet Response (20030212)



**Secondary Efficacy Results:** The secondary efficacy endpoints included overall platelet response, number of weeks with platelet response, proportion of subjects requiring rescuing medication and durable platelet response with stable dose. In both studies, Nplate group had significantly higher overall platelet response rates than placebo. Subjects of Nplate group had greater numbers of weeks with platelet response and higher durable platelet response rates with stable dose than placebo subjects in both studies.

On the other hand, more placebo subjects had required rescue medications during the treatment period than Nplate subjects. Table 7 presents the analysis results for the four secondary efficacy endpoint. Secondary efficacy analysis results from the two pivotal studies were consistent.

**Table 7 Secondary Efficacy Analysis Results, by Study**

	Study 20030105		
	Placebo (N=21)	Nplate (N=42)	p-value
<b>Overall platelet response</b>			
<b>Incidence rate</b>	0.0% (0/21)	78.6% (33/42)	<0.0001
<b>95% CI</b>	(0.0%, 16.1%)	(63.2%, 89.7%)	
<b>Number of weeks with platelet response</b>			
<b>Mean</b>	0.2 week	12.3 week	<0.0001
<b>SD</b>	0.5 week	7.9 week	
<b>Subjects requiring rescue medications</b>			
<b>Incidence rate</b>	57.1% (12/21)	26.2% (11/42)	0.0175
<b>95% CI</b>	(34.0%, 78.2%)	(13.9%, 42.0%)	
<b>Durable platelet response with stable dose</b>			
<b>Incidence rate</b>	0.0% (0/21)	31.0% (13/42)	0.0046
<b>95% CI</b>	(0.0%, 16.1%)	(17.6%, 47.1%)	
	Study 20030212		
	Placebo (N=21)	Nplate (N=41)	p-value
<b>Overall platelet response</b>			
<b>Incidence rate</b>	14.3% (3/21)	87.8% (36/41)	<0.0001
<b>95% CI</b>	(3.0%, 36.3%)	(73.8%, 95.9%)	
<b>Number of weeks with platelet response</b>			
<b>Mean</b>	1.3 week	15.2 week	<0.0001
<b>SD</b>	2.5 week	7.5 week	
<b>Subjects requiring rescue medications</b>			
<b>Incidence rate</b>	61.9% (13/21)	17.7% (7/41)	0.0004
<b>95% CI</b>	(38.4%, 81.9%)	(7.2%, 32.1%)	
<b>Durable platelet response with stable dose</b>			
<b>Incidence rate</b>	0.0% (0/21)	51.2% (21/41)	0.0001
<b>95% CI</b>	(0.0%, 16.1%)	(35.1%, 67.1%)	

### 3.2 Evaluation of Safety

More Safety evaluation can be seen in the medical reviewer's report.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race and Age

**Gender subgroup:** Table 13 shows the primary efficacy results, by gender subgroup. Treatment effect in favor to Nplate group was demonstrated in both female and male subgroups.

**Caucasian subgroup:** Majority of subjects in both two studies were Caucasians, 84.1% and 79.0% of subjects in 20030105 and 20030212, respectively. Table 14 shows the durable platelet response rates for Caucasian subjects in both arms of each study. It is obvious that the Nplate group consistently demonstrated treatment efficacy in the Caucasian subgroup.

Table 13 Durable Platelet Response Rates, by Gender and by Study

Study	Placebo	Nplate
20030105		
Female	0.0% (0/11)	40.7% (11/27)
Male	0.0% (0/17)	33.3% (5/15)
20030212		
Female	0.0% (0/10)	59.3% (16/27)
Male	20.0% (1/5)	64.3% (9/14)

Table 14 Durable Platelet Response for Caucasian subjects, by Study

Study	Placebo	Nplate
20030105		
Caucasians only	0.0% (0/19)	38.2% (13/34)
20030212		
Caucasians only	5.6% (1/17)	61.3% (19/31)

### 4.2 Other Special/Subgroup Populations

**Primary efficacy analysis by baseline concurrent ITP therapy:** Table 15 shows the results from analysis of the primary efficacy endpoint by subgroup of baseline concurrent ITP therapy (yes/no). Nplate group demonstrated treatment efficacy compared to placebo in both studies. The non-splenectomy subjects in Nplate group (Study 20030212) who had no baseline concurrent ITP therapy had 68.0% durable platelet response rate.

Table 15 Durable Platelet Response Rate, by Baseline ITP Therapy (Yes/No)

	Placebo	Nplate	p-value
Study 20030105 Baseline Concurrent ITP Therapy			
Yes	0.0% (0/7)	21.4% (3/14)	0.070
No	0.0% (0/14)	35.7% (10/28)	0.006
Study 20030212 Baseline Concurrent ITP Therapy			
Yes	12.5% (1/8)	50.0% (8/16)	0.074
No	0.0% (0/13)	68.0% (17/25)	<0.001

Note: P-values obtained from Chi-square test

No interim analysis was performed during the study ongoing time period. No blinding issues were reported in the submission.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The data obtained from the Nplate treated subjects of the two pivotal studies were pooled to assess the timing of the treatment effect and identify factors that might have influence on the platelet response. In Section 1.3, Table 3 presented the distribution of time to the first weekly platelet response (see page 5) showing that 85% of subjects in the durable platelet response group had their first weekly platelet response prior to Week 5.

In the following, Table 8 shows 39 out of 41 subjects (95%) in durable platelet response group having first platelet increase  $\geq 20,000/\mu\text{L}$  prior to Week 5. Table 9 shows 36 out of 41 subjects (90%) in durable platelet response group having 17 – 24 weeks of platelet responses during the Nplate treatment 24 week period. These two tables present consistent information as in Table 3.

Table 8 Distribution of Time to First Platelet Increase  $\geq 20,000/\mu\text{L}$

Time of First Weekly Platelet Response	Durable Platelet Response Group N=41	Transient Platelet Response Group N=28	Non-Responder N=14
1 <sup>st</sup> Week	22 (53.7%)	11 (39.3%)	2 (14.2%)
2 <sup>nd</sup> Week	8 (19.5%)	7 (25.0%)	0 (0.0%)
3 <sup>rd</sup> Week	5 (12.2%)	5 (17.9%)	0 (0.0%)
4 <sup>th</sup> Week	4 (9.8%)	2 (7.1%)	0 (0.0%)
5 <sup>th</sup> Week or Later	2 (4.9%)	3 (10.7%)	12 (85.8%)

Table 9 Distribution of Number of Weekly Platelet Response during the 24 Week Nplate Treatment Period

Number of Weekly Platelet Response during the 24 Week Treatment Period	Durable Platelet Response Group N=41	Transient Platelet Response Group N=28	Non-Responder N=14
0-4 Weeks	0 (0.0%)	1 (3.6%)	14 (100.0%)
5-8 Weeks	0 (0.0%)	6 (21.4%)	0 (0.0%)
9-12 Weeks	1 (2.4%)	10 (35.7%)	0 (0.0%)
13-16 Weeks	4 (9.6%)	6 (21.4%)	0 (0.0%)
17-20 Weeks	19 (46.3%)	4 (14.3%)	0 (0.0%)
21-24 Weeks	17 (41.5%)	1 (3.6%)	0 (0.0%)

Table 10 shows mean and standard deviation of time to first weekly platelet response, time to first platelet increase  $\geq 20,000/\mu\text{L}$ , peak platelet, and number of previous ITP treatment. Table 11 shows the status of splenectomy by platelet response group.

Table 10 Mean Time to First Weekly Platelet Response, Mean Time to First Platelet Increase  $\geq 20,000/\mu\text{L}$ , Mean Peak Platelet, and Mean Number of Previous ITP Treatment

	Durable Platelet Response Group N=41	Transient Platelet Response Group N=28	Non-Responder N=14
Mean Time to First Weekly Platelet Response	2.5 $\pm$ 1.8 weeks	3.4 $\pm$ 3.1 weeks	16.4 $\pm$ 8.8 weeks
Mean Time to 1 <sup>st</sup> Platelet Increase $\geq 20,000/\mu\text{L}$	2.0 $\pm$ 1.4 weeks	2.6 $\pm$ 2.5 weeks	15.6 $\pm$ 9.0 weeks
Mean Peak Platelet	228.0 $\pm$ 115.9	286.7 $\pm$ 195.4	83.8 $\pm$ 114.3
Mean Number of Previous ITP Treatment	3.7 $\pm$ 1.9	4.9 $\pm$ 2.3	6.2 $\pm$ 2.3

Table 11 Status of Splenectomy by Platelet Response Group

Study	Durable Platelet Response Group N=41	Transient Platelet Response Group N=28	Non-Responder N=14
20030105	16 (39.0%)	17 (60.7%)	9 (64.3%)
20030212	25 (61.0%)	11 (39.3%)	5 (35.7%)

In order to identify the factors that could have impact on the non-responsiveness of Nplate treatment, logistic regression analysis was performed. Non-responder vs. durable/transient response was the outcome variable in the logistic regression model. Number of previous ITP therapy, time to first weekly platelet response and status of splenectomy were input variables, adjusted for age and gender. Time to first weekly platelet response was dichotomized with the cutoff of 4<sup>th</sup> week and 5<sup>th</sup> week plus.

Results showed that number of previous ITP therapy and time to first weekly platelet response were statistically significant in the logistic regression model. The odds ratio and corresponding 95% confidence interval can be seen in Table 12.

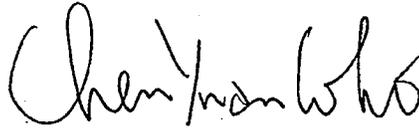
Table 12 Odds Ratio and 95% Confidence Interval from Logistic Regression analysis

	Odds Ratio	95% CI
Previous ITP therapy	1.97	(1.13, 3.42)
Time to 1st Weekly Platelet Response	49.06	(6.09, 395.32)
Status of Splenectomy	13.88	(0.91, 211.73)

The results from analyzing the primary endpoint had shown the significant treatment efficacy. Subgroup analyses also presented robust results. The results from analyzing the four secondary efficacy endpoints provided with supportive evidence of efficacy. Studies 20030105 and 20030212 were the first two clinical pivotal trials in the history using experimental therapy to assess the efficacy in the treatment of patients with ITP.

## 5.2 Conclusions and Recommendations

Based upon the efficacy results presented by the sponsor and this reviewer's statistical evaluation of the two pivotal studies, the applicant has provided sufficient evidence of significant efficacy of Nplate in the treatment of patients with chronic idiopathic thrombocytopenic purpura. One of the two pivotal studies enrolled subjects who were non-splenectomized and had an inadequate response to corticosteroids and/or immunoglobulins. The other study enrolled subjects who were splenectomized and had an inadequate response to splenectomy. The efficacy results from the two pivotal studies support the indication claim.

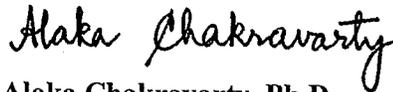


**Primary Statistical Reviewer:** Yuan Who Chen, Ph.D.  
**Date:** April 14, 2008

**Concurring Reviewer(s):**



**Statistical Team Leader:** Jyoti Zalkikar, Ph.D.



**Biometrics Division Director:** Aloka Chakravarty, Ph.D.

**cc:**  
HFD-109/Florence Moore  
HFD-160/Dr. Faranak Jamali  
HFD-160/Dr. Kathy Robie-Suh  
HFD-160/Dr. Rafel Rieves  
HFD-745/Dr. Jyoti Zalkikar  
HFD-745/Dr. Aloka Chakravarty

c:\NDA\statreview.doc