6.2 Proposed Indication

The primary indication sought by the Applicant is treatment of thrombocytopenia in adult patients with chronic ITP, who are:

- Nonsplenectomized and have had an inadequate response or are intolerant to corticosteroids and/or immunoglobulins, or
- Splenectomized and have had an inadequate response to splenectomy.

6.3 Methods

The two controlled phase 3 studies submitted by the applicant were: study 1 (in non splenectomized patients) and study 2 (in splenectomized patients). Both studies were multicenter, double-blind, placebo- controlled and patients were randomized (2:1; active: placebo). The 3rd study was the ongoing, uncontrolled open-label extension study conducted in patients who had completed an earlier NPLATE study. The objective of the extension study was to assess both safety and efficacy of the long term dosing of Nplate.

The study patients had at least one prior ITP medication prior to enrollment. Study drug was administered for 24 weeks followed by 12 weeks of non- administration of study drug and evaluation of patients at the end of 36 weeks of study in the two phase 3 controlled studies.

The protocol for the two phase 3 and extension studies are summarized below:

Protocol Summary for Study 1 (non-splenectomized) and Study 2 (splenectomized)

Objectives:

The primary objective of both controlled studies was to evaluate the efficacy of Nplate in the treatment of thrombocytopenia in subjects with ITP who had not undergone splenectomy (study 1) and in subjects who were refractory to splenectomy (study 2) as measured by the durable platelet response during the last 8 weeks of treatment and other platelet response parameters.

The secondary objectives were the overall safety of Nplate, reductions in the dose of concurrent ITP therapies while receiving Nplate and changes in patient reported outcomes and health resource utilization due to treatment with Nplate.

Study Drug Administration and Dose Adjustment:

The study drug was administered subcutaneously (SC) once per week at a starting dose of 1 µg/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 x 10^9/L. The maximum permitted dose was 15 µg/kg. After 24 weeks of treatment, investigational product was withdrawn and the platelet count monitored. Participation was complete once platelet counts

were ≤ 50 x10^9/L or the subject reached week 36 with a platelet count > 50 x109/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 x 10^9/L. Pre-dose sampling for pharmacokinetic (PK) studies were performed once the patient reached a dose of ≥ 10 µg/kg/week.

In both pivotal and extension studies starting dose was 1 mcg/kg per week administered subcutaneously. Dose adjustments were made according to table 3 and table 4.

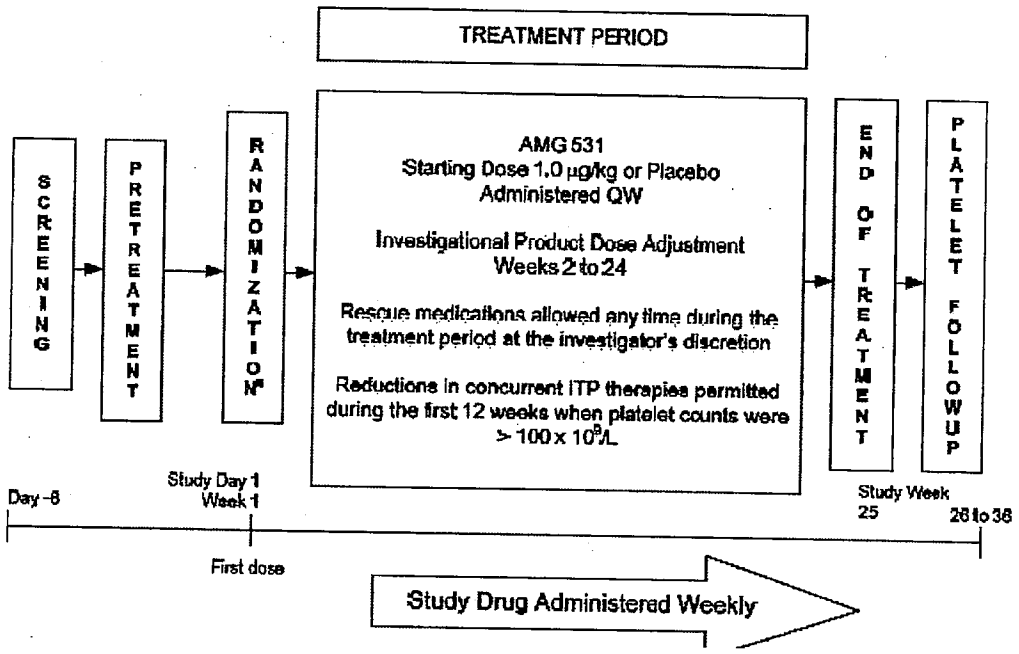
Table 3: Dose Adjustment in Pivotal Studies (Study 1 and 2)

Platelet Count (x 10^9/L)	Action
Start-up (to a platelet count of > 50 x 10^9/L):	
≤ 10	Dose increase by 2 µg/kg every week in which counts ≤ 10 x 10^9/L; can be increased every week.
> 10 to ≤ 50	Dose increase by 2 µg/kg after 2 consecutive weeks of counts ≤ 50 x 10^9/L; can be increased every 2 weeks.
> 50	Dose remains constant on weekly schedule; maintenance rules below.
Maintenance (once platelet count > 50 x 10^9/L):	
≤ 10	Dose increase by 1 µg/kg every week in which counts ≤ 10 x 10^9/L; can be increased every week.
> 10 to ≤ 50	Dose increase by 1 µg/kg after 2 consecutive weeks of counts in this range. Dose can be increased every 2 weeks.
> 50 to ≤ 200	Dose constant
> 200 to ≤ 400	Dose reduced by 1 µg/kg after 2 consecutive weeks of platelet counts in this range. Dose can be reduced every 2 weeks.
> 400	Next scheduled dose held, and dose reduced by 1 µg/kg on next scheduled dosing day on which count ≤ 200 x 10^9/L.

Study Plan:

The study plan for the two controlled clinical trials is shown below:

Figure 1: Study Plan for controlled clinical trials (study 1 and 2)



Subject Selection:

Entry criteria were the same in both of the pivotal studies.

Inclusion Criteria:

Subjects were required to be at least 18 years old with a diagnosis of ITP according to American Society of Hematology (ASH) guidelines (George et al, 1996); Subjects must have completed at least 1 previous treatment for ITP and had a mean of 3 platelet counts during screening and pre-treatment that was $\leq 30 \times 10^9$/L, with no individual count $> 35 \times 10^9$/L. Hemoglobin of at least 9.0 g/dL was required at baseline to ensure a single lineage deficiency. Subjects over 60 years of age were required to have a documented history of chronic ITP with a bone marrow report in order to exclude myelodysplastic syndromes. Those with a known history of bone marrow stem cell disorder were excluded. In study 2, splenectomy was required to have occurred at least 4 weeks before study entry.

Exclusion Criteria:

Subjects were excluded for any known history of bone marrow stem cell disorder, any active malignancy. in patients with prior history of cancer other than basal cell carcinoma or cervical carcinoma in situ, receiving any treatment or active disease within 5 years before randomization, currently receiving any treatment for ITP, except for corticosteroids, azathioprine, or danazol administered at a constant dose and schedule , IVIG or anti-D Immunoglobulin within 2 weeks before screening, Rituximab (for any indication) within 14 weeks before screening or anticipated use during the time of the proposed study, received hematopoietic growth factors, including IL-11(oprelvekin) within 4 weeks before the screening visit, past or present participation in any study evaluating PEG-rHuMGDF, recombinant human thrombopoietin (rHuTPO), Nplate, or related platelet product, received any alkylating agents within 8 weeks before the screening visit or anticipated use during the time of the proposed study, less than 4 weeks since receipt of any therapeutic drug or device that is not FDA approved for any indication before the screening period, pregnant or breast feeding or not using adequate contraceptive precautions, subjects of reproductive potential who are not using adequate contraceptive precautions and known hypersensitivity to any recombinant E. coli derived product.

Summary of the extension study (study 3) protocol

The extension study was an ongoing, multicenter, open-label, study of Nplate. The primary objective of this study is to evaluate the safety of Nplate as a long-term treatment in thrombocytopenic subjects with immune (idiopathic) thrombocytopenic purpura (ITP). The secondary objectives are to evaluate the long-term platelet response to Nplate; to evaluate reductions in the dose of concurrent ITP therapies while receiving Nplate; and to evaluate changes in patient reported outcomes (PROs) due to the use of Nplate.

Study Plan

Subjects who completed an ITP study with Nplate were eligible to screen for inclusion in this study; subjects were not eligible unless their platelet counts were $\geq$ 50 x 109/L. Nplate was administered subcutaneously (SC) once weekly and individual-subject dose adjustment was allowed throughout the study according to pre-defined rules based on a subject's platelet counts (see table 4). Subjects for whom the dose of Nplate was the same for at least 3 weeks were allowed to self-inject Nplate away from the study center and were instructed to return to the study center for ongoing evaluation at designated study visits. When a subject discontinued Nplate for any reason, the subject was to complete end-of-study assessments 1 week after the last dose of Nplate. Rescue medication was permitted for bleeding or wet purpura, when platelet counts were $< 10 \times 10^9$/L, or in any situation if deemed medically necessary by the investigator. Reductions in concurrent ITP therapies could occur at any time when platelet counts were $> 50 \times 10^9$/L.

Table 4: Dose Adjustment in Extension Study (Study 3)

Platelet Count ($\times 10^9$/L)	Action
≤ 10	Dose increased by 2 µg/kg every week when platelet counts are ≤ 10. Dose can be increased every week.
> 10 to < 50	Dose increased by 2 µg/kg after two consecutive weeks of platelet counts <50. Dose can be increased every two weeks.
50 to 250	Dose may be adjusted by 1 µg/kg (increased or decreased) at the investigators discretion, no more frequently than every two weeks. The maximum dose is 10 µg/kg weekly.
> 250 to < 400	Dose reduced by 1 µg/kg after two consecutive weeks of platelet counts in this range. Dose can be reduced every two weeks.
≥ 400	Next scheduled dose held, and the dose will be reduced by 1 µg/kg on the next scheduled dosing day that the platelet count is < 250 x 10^9/L.

6.4 Study Endpoints

The primary endpoint for both phase 3 controlled studies was the proportion of patients achieving a durable platelet response.

The secondary Endpoints are listed below:

- Incidence of overall platelet response (durable and transient)
- Number of weekly platelet responses
- Proportion of patients requiring rescue medication
- Incidence of durable platelet response on stable dose

The following represents a list of endpoint definitions:

- Durable Response: Platelet counts $\geq 50 \times 10^3$/uL for ≥ 6 weeks during the last 8 weeks of treatment with no rescue medication use at any time during treatment.
- Transient Response: Platelet counts $\geq 50 \times 10^3$/uL for ≥ 4 weeks between weeks 2 and 25 in the absence of a durable platelet response
- Overall Response: Achieving either of the two mutually exclusive response types (transient response or durable response)
- Non-Response: Fewer than 4 weekly platelet counts $\geq 50 \times 10^3$/uL between weeks 2 and 25
- Stable dose: Dose within 1 μg/kg during the last 8 weeks of treatment (weeks 17 to 24)

The primary endpoint for the extension study was safety (incidence of adverse events).

6.5 Data Analysis:

The efficacy analysis included all patients who were randomized in studies 1 or 2 who took at least 1 dose of the study drug. Safety was compared between Nplate and placebo. The incidences of durable and overall platelet responses, proportion of subjects requiring rescue medication, and incidence of achieving stable dose were compared between the Nplate and placebo groups. The number of weeks with platelet response for both treatment groups was summarized and compared.

6.6 Results

6.6.1 Patient Disposition

There were a total of 125 patients enrolled and in the two phase 3 trials. Forty two of these patients were randomized to receive placebo and 83 were randomized to receive Nplate (see Tables 5).

Table 5: Disposition of Patients in controlled Phase 3 Studies

	Study 1 (non splenectomized patients)		Study 2 (splenectomized patients)		Both Studies		
	Placebo n (%)	Nplate n (%)	Placebo n (%)	Nplate n (%)	Placebo n (%)	Nplate n (%)	Total
Randomized to Phase 3 Study	21 (100)	41 (100)	21(100)	42 (100)	42 (100)	83(100)	125(100)
Discontinued	4 (19)	2 (4.9)	2 (9.5)	2 (4.8)	6 (14.3)	4 (4.8)	10 (8)
Completed	17 (81)	39 (95)	19 (90.5)	40 (95.2)	36 (85.7)	79 (95.2)	115 (92)

Reviewer Comment: As shown in the table a total of 115 (92%) subjects (85.7% placebo and 95.2% Nplate) completed the study. 6 (14.3%) of patients in placebo and 4(4.8%) patients in the comparator group discontinued from the study.

6.6.2 Patient Distribution by Region

Patients' distribution in the controlled phase 3 trials by region is summarized below:

Table 6: Numbers of Patients in Phase 3 Studies by Region

	Study 1 (non splenectomized patients)		Study 2 (splenectomized patients)		Both Studies		Total
	Placebo (N = 21) n (%)	Nplate (N = 41) n (%)	Placebo (N = 21) n (%)	Nplate (N = 42) n (%)	Placebo (N = 42) n (%)	Nplate (N = 83) n (%)	(N = 125) n (%)
North America	17 (81.0)	37 (90.2)	17 (81.0)	32 (76.2)	34 (81)	69 (83.1)	103 (82)
United States	17 (81.0)	37 (90.2)	17 (81.0)	32 (76.2)	34(81.0)	69 (83.1)	103 (82)
European Union	4 (19.0)	4 (9.8)	4 (19.0)	10 (23.8)	8 (19.0)	14 (16.9)	22 (17.6)
France	2 (9.5)	0 (0.0)	0 (0.0)	5 (11.9)	2 (4.8)	5 (6.0)	7 (5.6)
Netherlands	0 (0.0)	1 (2.4)	3 (14.3)	1 (2.4)	3 (7.1)	2 (2.4)	5 (4.0)
Spain	1 (4.8)	3 (7.3)	0 (0.0)	3 (7.1)	1 (2.4)	6 (7.2)	7 (5.6)
United Kingdom	1 (4.8)	0 (0.0)	1 (4.8)	1 (2.4)	2 (4.8)	1 (1.2)	3 (2.4)

Reviewer Comment: Majority of patients were from the United States (83%).

6.6.3 Demographics

Patient demographics, baseline hematology, thrombopoietin (TPO) levels, and ITP treatment history are shown in Table 7, Table 8 and Table 9.

A total of 125 male and female subjects, 18 months to ≥ 65 years of age, who received at least 1 dose of Nplate or placebo were enrolled in the studies.

Table 7: Demographics of Patients in Phase 3 Studies

	Study 1 (non splenectomized patients)		Study 2 (splenectomized patients)		Both Studies		Total N = 125
	Placebo (N = 21)	Nplate (N = 41)	Placebo (N = 21)	Nplate (N = 42)	Placebo (N = 42)	Nplate (N = 83)	
Age Group in Years - n (%)							
18-29	3 (14.3)	2 (4.9)	2 (9.5)	3 (7.1)	5 (11.9)	5 (6.0)	10 (8.0)
30-39	3 (14.3)	5(12.2)	1 (4.8)	10(23.8)	4 (9.5)	15 (18.1)	19 (15.2)
40-49	5 (23.8)	10(24.4)	4 (19.0)	8 (19.0)	9 (21.4)	18 (21.7)	27 (21.6)
50-59	1 (4.8)	11(26.8)	5 (23.8)	8 (19.0)	6 (14.3)	19 (22.9)	25 (20.0)
60-64	1 (4.8)	5 (12.2)	4 (19.0)	3 (7.1)	5 (11.9)	8 (9.6)	13 (10.4)
≥ 65	8 (38.1)	8 (19.5)	5(23.8)	10(23.8)	13(31.0)	18 (21.7)	31 (24.8)
Age (years)							
n	21	41	21	42	42	83	125
Mean	55.0	53.3	53.9	51.1	54.5	52.2	53.0
SD	21.7	15.5	13.4	15.6	17.8	15.5	16.3
Median	46.0	52.0	56.0	50.5	52.0	52.0	52.0
Q1, Q3	39.0, 73.0	41.0, 63.0	46.0, 62.0	38.0, 64.0	43.0, 70.0	40.0, 63.0	40.0, 64.0
Min, Max	23, 88	21, 80	26, 72	27, 88	23, 88	21, 88	21, 88
Sex - n (%)							
Male	5 (23.8)	14(34.1)	10(47.6)	15(35.7)	15(35.7)	29 (34.9)	44 (35.2)
Female	16(76.2)	27(65.9)	11(52.4)	27(64.3)	27(64.3)	54(65.1)	81 (64.8)
Race - n (%)							
White or Caucasian	18(85.7)	31(75.6)	19 90.5)	34(81.0)	37 (88.1)	65 (78.3)	102 (81.6)
Black or African American	1 (4.8)	3 (7.3)	2 (9.5)	3 (7.1)	3 (7.1)	6 (7.2)	9 (7.2)
Hispanic or Latino	2 (9.5)	3 (7.3)	0 (0.0)	3 (7.1)	2 (4.8)	6 (7.2)	8 (6.4)
Asian	0 (0.0)	3 (7.3)	0 (0.0)	2 (4.8)	0 (0.0)	5 (6.0)	5 (4.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	1 (0.8)

Medical Reviewer Comment: 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%). Asians included only 4% of the study population. There were no clinical important differences in any of the baseline demographic characteristics between the two treatments.

Since majority of patients were Caucasians, generalization about study results may not be made in other races.

Table 8: Baseline Hematology and Endogenous Thrombopoietin (Phase 3 Studies)

	Study 1 (non splenectomized patients)		Study 2 (splenectomized patients)		Both Studies		Total
	Placebo (N = 21)	Nplate (N = 41)	Placebo (N = 21)	Nplate (N = 42)	Placebo (N = 42)	Nplate (N = 83)	(N = 125)
Platelet Count (10^9/L)							
n	21	41	21	42	42	83	125
Mean	19.1	17.9	14.1	15.0	16.6	16.4	16.5
SD	8.3	7.6	8.1	7.8	8.5	7.8	8.0
Median	19.3	18.7	14.7	13.5	17.7	15.7	16.0
Min, Max	5, 31	2, 29	2, 28	3, 29	2, 31	2, 29	2, 31
Red Blood Cells (10^{12}/L)							
n	20	41	21	42	41	83	124
Mean	4.43	4.53	4.55	4.53	4.49	4.53	4.52
SD	0.60	0.56	0.53	0.53	0.56	0.55	0.55
Median	4.45	4.52	4.64	4.57	4.60	4.55	4.55
Min, Max	3.1, 5.4	3.4, 5.8	3.3, 5.4	3.1, 5.5	3.1, 5.4	3.1, 5.8	3.1, 5.8
White Blood Cells (10^9/L)							
n	20	41	21	42	41	83	124
Mean	7.70	6.63	9.64	10.42	8.69	8.55	8.59
SD	3.74	3.04	4.87	4.81	4.41	4.44	4.41
Median	7.70	5.87	8.40	8.94	8.20	7.30	7.66
Min, Max	2.9, 18.7	2.6, 16.2	4.2, 26.9	3.6, 21.4	2.9,26.9	2.6, 21.4	2.6,26.9
Hemoglobin g/dl							
n	20	41	21	42	41	83	124
Mean	128.50	136.66	142.24	136.29	135.54	136.47	136.16
SD	16.45	14.64	18.77	16.00	18.79	15.25	16.43
Median	125.00	136.00	145.00	137.00	133.00	137.00	137.00
Min, Max	103.0, 165.0	105.0, 160.0	89.00, 177.0	91.0, 174.0	89.0, 177.0	91.0, 174.0	89.0, 177.0

Medical Reviewer Comment: The baseline median platelet counts were 18 (range 2 - 31) x 10^3/uL in the placebo group and 16 (range 2 - 29) x 10^3/uL in the Nplate group. Median values for RBC, WBC, hemoglobin, and endogenous thrombopoietin were balanced between the two treatment groups and across the two studies. Compared to patients in the non-splenectomized study, the patients enrolled in the splenectomized studies had slightly lower median platelet counts.

Table 9: ITP Treatment History (Phase 3 Study Subjects)

	Study 1 (non splenectomized patients)		Study 2 (splenectomized patients)		Both Studies		Total
	Placebo (N = 21)	Nplate (N = 41)	Placebo (N = 21)	Nplate (N = 42)	Placebo (N = 42)	Nplate (N = 83)	(N = 125)
Number of Subjects with Prior ITP Treatment - n (%)							
Corticosteroid	19 (90.5)	37(90.2)	20 (95.2)	42 (100.0)	39 (92.9)	79(95)	118(94)
Immunoglobin	18 (85.7)	29(70.7)	20 (95.2)	41 (97.6)	38 (90.5)	70(84)	108(86)
Anti-D Antibody (WinRho)	6(28.6)	20(48.8)	9(42.9)	19 (45.2)	15 (35.7)	39(47)	54 (43)
IVIG	15 (71.4)	26(63.4)	20 (95.2)	39 92.9)	35 (83.3)	65(78)	100(80)
Chemotherapy	7(33.3)	6(14.6)	17 (81.0)	26 (61.9)	24 (57.1)	32 (39)	56 (45)
Vinscristine/vinblastine	0(0.0)	0(0.0)	10 (47.6)	17 (40.5)	10 (23.8)	17 (21)	27 (22)
Cyclophosphamide	7(33.3)	6(14.6)	14 (66.7)	21 (50.0)	21 (50.0)	27 (33)	48 (38)
Azathioprine	1(4.8)	2(4.9)	5 (23.8)	10 (23.8)	6(14.3)	12(15)	18(14)
Danazol	1(4.8)	6(14.6)	10 (47.6)	13 (31.0)	11 (26.2)	19(23)	30 (24)
Rituximab	5(23.8)	13(31.7)	15 (71.4)	30 (71.4)	20 (47.6)	43(52)	63 (50)
Other	6(28.6)	10(24.4)	11 (52.4)	21 (50.0)	17 (40.5)	31(37)	48 (38.)
Splenectomized Subjects - n (%)	0(0.0)	0(0.0)	21 (100.0)	42 (100.0)	21 (50.0)	42(51)	63 (50)
Total Number of ITP Treatments Subject Ever Received- n (%)							
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	2(9.5)	9(22.0)	0(0.0)	0(0.0)	2(4.8)	9 (10.8)	11 (9)
2	9(42.9)	9(22.0)	0(0.0)	0(0.0)	9(21.4)	9 (10.8)	18 (14)
3	5(23.8)	8(19.5)	1(4.8)	3(7.1)	6(14.3)	11 (13)	17 (14)
4	2(9.5)	9(22.0)	1(4.8)	7(16.7)	3(7.1)	16 19.3)	19 (15)
5	2(9.5)	4(9.8)	4(19.0)	9(21.4)	6(14.3)	13(16)	19 (15)
6	0(0.0)	1(2.4)	5(23.8)	6(14.3)	5(11.9)	7(8.4)	12 (10)
7	1(4.8)	1(2.4)	4(19.0)	6(14.3)	5(11.9)	7(8.4)	12 (10)
8	0(0.0)	0(0.0)	5(23.8)	5(11.9)	5(11.9)	5(6.0)	10 (8.0)
9	0(0.0)	0(0.0)	0(0.0)	6(14.3)	0(0.0)	6(7.2)	6(4.8)
10	0(0.0)	0(0.0)	1(4.8)	0(0.0)	1(2.4)	0(0.0)	1(0.8)

Medical Reviewer Comment: Per patient selection criteria, all patients had received at least 1 previous ITP therapy: most (94%) patients had received corticosteroids and most patients (66% in study 212, 94% in study 105) had received IVIG. All patients had been treated and failed current first-line therapies for ITP.

6.6.4 Efficacy Analysis

The primary endpoint was the durable platelet response defined as platelet counts > 50 x 10^3/uL for > 6 weeks during the last 8 weeks of treatment with no rescue medication use at any time during treatment.

Overall durable platelet response & overall platelet response are summarized in Table 10 & Table 11.

Table 10: Results of Durable Platelet Responses from Placebo-Controlled Studies

Outcome	Study 1 (non splenectomized patients)		Study 2 (splenectomized patients)		p-value*
	Placebo n = 21	Nplate n = 41	Placebo n = 21	Nplate n = 42	
Durable platelet response, n (primary EP)	1(5%)	25(61%)	0 (0%)	16 (38%)	< 0.01*

*p-value was similar for each study

Medical Reviewer Comment: A significantly greater proportion of patients in the Nplate group achieved the primary endpoint, durable platelet response than in the placebo group. The results obtained in patients who had not undergone splenectomy were consistent with those obtained in patients who had undergone splenectomy. In general, the response rates (proportions of patients) in patients who have not undergone splenectomy (both placebo and Nplate groups) were higher than the response rates in patients who have undergone splenectomy (corresponding treatment groups).

Nplate appears to be 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).

Table 11: Summary of the overall platelet response, n (%), number of weeks with platelet counts ≥ 50 x 10^9/L, average and patients requiring rescue therapy, n (%)

Outcomes	Study 1 Non-splenectomized Patients		Study 2 Splenectomized Patients	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)
Overall Platelet Response, n (%)	36 (88%)	3 (14%)	33 (79%)	0 (0%)
Number of Weeks with Platelet Counts ≥ 50 x 10^9/L, average	15	1	12	0
Requiring Rescue Therapy, n (%)	7 (17%)	13 (62%)	11 (26%)	12 (57%)

Medical Reviewer Comment: A significantly greater proportion of patients in the Nplate group achieved the secondary endpoints (overall platelet response, number of weeks with platelet counts≥ 50 x 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.

The reduction/discontinuation of baseline concurrent ITP medical therapy in the phase 3 trials was compared. Table 12 compares the reduction/discontinuation of baseline concurrent ITP medical therapy in the two treatment groups:

Table 12: Reduction/Discontinuation of Baseline Concurrent ITP Medical Therapy

	Study 1 Non-splenectomized Patients		Study 2 Splenectomized Patients	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)
Receiving Therapy at Baseline	11	10	12	6
Patients who had > 25% Dose Reduction in Concurrent Therapy n (%)	4/11 (36%)	2/10 (20%)	4/12 (33%)	1/6 (17%)
Patients who Discontinued Baseline Therapy n (%)	4/11 (36%)	3/10 (30%)	8/12 (67%)	0/6 (0%)

Medical Reviewer's comment: Numerically greater number of patients in Nplate group had > 25% dose reduction in concurrent therapy and discontinued baseline therapy as compare patients who received placebo. However a definitive conclusion may not be made since the number of patients who received baseline therapy was small.

Bleeding Events

The incidence rate of any bleeding adverse event and any serious bleeding events are described in Table 13.

Table 13: 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%)

Reviewer's comment: An association between any bleeding event and achievement of durable platelet response was not observed, since the incidence rate of any bleeding event was similar between Nplate and placebo. The observed difference in any serious bleed between Nplate and placebo group was numerically small.

6.6.5 Subpopulations

There are no adequate and well-controlled studies of Nplate use in pregnant women, nursing mothers, pediatric patients, patients with renal or hepatic impairment.

Geriatric Use

Of the 271 patients who received Nplate in ITP clinical studies, 38 (19%) were age 65 and over, and 18 (9%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies.

6.6.6 Analysis of Clinical Information Relevant to Dosing Recommendations

Four dose finding studies were conducted using either a weight-based dose or fixed doses to evaluate the PK and platelet profiles of Nplate in subjects with chronic ITP. Achievement of the target platelet response (defined as the peak platelet count achieving a doubling of baseline platelet and within the range of $\geq 50x10^9$/L and $\leq 450x10^9$/L, in the absence of rescue medication) was dose-dependent. Dose-finding studies identified the starting dose of 1 mcg/kg and weekly dosing schedule based on the patient platelet responses. This initial dose followed by the dose adjustment with increments of 1 mcg/kg based on the platelet count. The most frequently used weekly dose of Nplate for non-splenectomized patients was between 1-3 mcg/kg (25th–75th percentile; median: 2 mcg/kg), and for splenectomized patients was between 2-7 mcg/kg (25th–75th percentile; median: 3 mcg/kg).

Dose-Response Relationship: Both the exposure of Nplate and the platelet response (PD) are dependent on the dose administered and the baseline platelet count. A linked PK/PD model was developed for Nplate, which incorporated receptor-mediated distribution and elimination to describe Nplate disposition. In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet count. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with chronic ITP, the peak platelet counts were 1.3 to 14.9 times greater than the baseline platelet counts over a 2 to 3 week period. In a study, the platelet counts of patients with chronic ITP who received six weekly doses of 1 mcg/kg Nplate were within the range of 50 to 450 $x10^9$/L for 7 out of 8 patients.

Pharmacokinetics (PK) of Nplate: The pharmacokinetics of Nplate was studied in healthy subjects after intravenous Nplate administration. Systemic exposure to Nplate (C0 and AUC0-t) increased more than proportionally with dose. This finding was consistent with the target-mediated disposition. Nplate presumably binds to c-Mpl on platelets and other cells in the thrombopoiesis lineage, such as megakaryocytes, and is subsequently internalized and degraded inside these cells. The mean elimination half-life was short and increased with dose (1.5, 2.4 and 13.8 hours for doses of 0.3, 1 and 10 mcg/kg, respectively). The characterization of PK in healthy subjects after subcutaneous administration of Nplate was not successful due to non measurable concentrations in most samples after 0.1, 0.3, 1 and 2 mcg/kg doses. In the long-term extension study in patients with chronic ITP who received weekly treatment of Nplate subcutaneously over the dose range of 3 to 15 mcg/kg,

peak serum concentrations were observed around 7 to 50 hrs postdose (median: 14 hrs) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum Nplate is in part dependent on the c-Mpl receptor on platelets. As a result, for a given dose, patients with high platelet counts were associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum Nplate concentrations was observed after six weekly doses of 3 mcg/kg of Nplate.

No hepatic or renal studies have been conducted with Nplate. The safety and effectiveness of Nplate in pediatric patients (< age 18) have not been established. It is not known whether Nplate is excreted in human milk.

For details of clinical pharmacology issues, please refer to Drs. Angela Men and Hong Zhao's review.

6.6.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

See section 6.6.2 for this information.

6.6.8 Additional Efficacy Issues/Analyses

Extension Study (Study 3):

This was an ongoing, multicenter, open-label, 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).

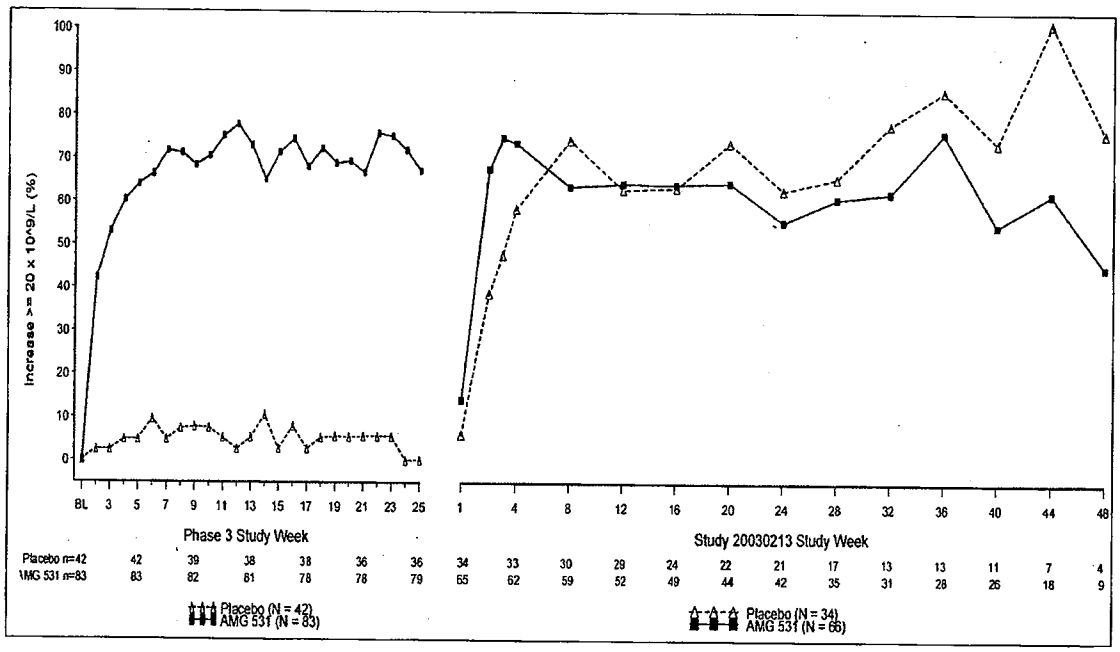
The secondary endpoints are incidence of platelet response (platelet response is defined as a doubling of baseline platelet count and platelet count $\geq 50 \times 10^9$/L in the absence of rescue Medication) within the preceding 8 weeks and reduction in the dose or discontinuation of concurrent ITP therapies while receiving Nplate.

The results obtained from the uncontrolled long-term extension study are discussed below. The safety results from the extension study are included in the integrated review of safety.

The baseline demographic characteristics and patient disposition in the extension study was similar to the two controlled phase 3 studies.

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. Figure 2 demonstrates the change in platelet count > 20 ($\times 10^3$/uL) above baseline in controlled studies and in uncontrolled long-term extension study.

Figure 2: Change in platelet count > 20 (x 10^3/uL) above baseline, in controlled studies (pooled data, left panel) and in uncontrolled long-term extension study (right panel).



AMG 531= Nplate

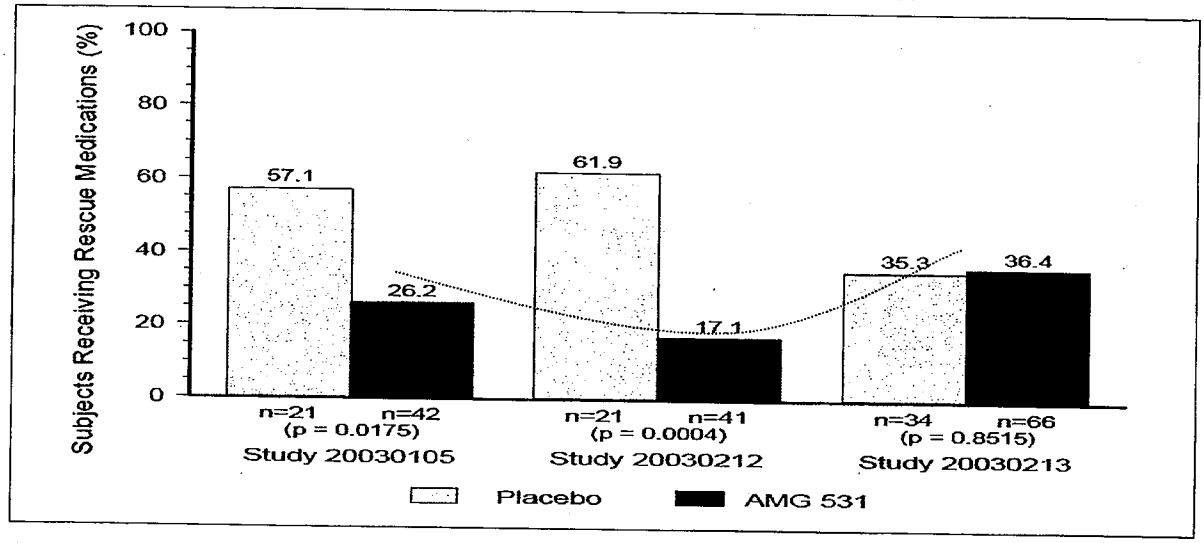
During the first 30 weeks of Nplate therapy, the response rates (proportions of patients) over time among "placebo patients" in study 3 (previously randomized to placebo in controlled studies, but on Nplate in study 3; dashed curve, right panel) parallel the response rates in patients randomized to Nplate in controlled studies (solid curve, left panel).

Beyond 30 weeks, the response rates in the "placebo patients" (previously randomized to placebo in controlled studies) appear to exceed modestly the response rates in patients randomized to Nplate in controlled studies. The apparent greater response rates in placebo patients may have resulted from a more liberal dosing guideline used in the extension study and/or loss of therapeutic effect over time in the Nplate group due to decline in treatment-induced thrombopoiesis with prolonged use of Nplate (about one year, between two studies).

The initial rate of rise in the response curve for the "Nplate patients" in the extension study (solid curve, right panel) exceeds those for the "placebo patients" in the extension study (dashed curve, right panel) and for the patients randomized to Nplate in controlled studies (solid curve, left panel). The more rapid rate of rise in previously treated patients likely reflects the dosing guideline used in the extension study, which permitted previously determined stable doses in controlled studies as the starting doses in the extension study.

Comparison of the use of rescue medication in extension study versus controlled studies is shown below:

Figure 3: Use of Rescue Medication (Phase 3 Studies and extension study)



AMG 531= Nplate

As might be expected, 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. Among patients receiving Nplate therapy, the proportion of patients requiring rescue medication appears to be significantly greater in the extension study than in controlled studies (see figure 3). This may be related to with prolonged use of Nplate and decline in efficacy over time.

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7 Review of Safety

The safety data were reviewed with particular reference to the occurrence of adverse events. Safety evaluations for this study included assessments of duration of study drug exposure, serious adverse events and adverse events (serious and nonserious). The analyses of safety included all assigned patients who received any amount of study drug.

7.1 Methods

The safety database includes 271 patients with chronic ITP who received at least one dose of Nplate.

Safety was assessed by integrating the data of the applicant-sponsored trials. Study reports, line listings, and Case Report Forms were reviewed. The safety review also consisted of a review of all adverse events including laboratory abnormalities by summary tables and line listings, along with review of physical examination line listings. The review integrated the 120 day safety update.

7.1.1 Clinical Studies Used to Evaluate Safety

A total of 271 patients with chronic ITP were exposed to Nplate during the development program. The clinical data sources used for safety assessment are shown in table 14.

Table 14: Subject Disposition Across Safety Analysis Sets

Safety Set	Total number of Subjects
Phase 3 ITP safety set	125
Phase 3 ITP long-term safety set	125
Marketing application ITP safety set	229
Comprehensive ITP safety set	308[a]

[a]A total of 271 out of 308 ITP patients were exposed to Nplate.

7.1.2 Adequacy of Data

The data submitted was adequate for review. All adverse events were coded by system organ class and preferred term according to the Medical Dictionary of Drug Regulatory Affairs (MedDRA, version 9.0). The incidence of adverse events was summarized by system organ class and preferred term for each treatment group according to MedDRA, version 9.0. The methods that were used to code adverse events were adequate.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Both in the original and in the 120 day safety update submissions, sponsor has used various safety sets, i.e., phase 3 ITP safety set, phase 3 ITP long-term safety set , marketing application ITP safety set, and comprehensive ITP safety sets (see section 7.1.1).

7.2 Adequacy of Safety Assessments

In order to evaluate the safety of the drug sponsor has performed most tests reasonably applicable during the study periods. However, the duration of exposure in the two phase III placebo-controlled studies is only 24 weeks and the median duration of exposure in the entire chronic ITP safety database is approximately 37 weeks with only 36 patients having an exposure of at least 2 years. Therefore, long term safety data are limited. In addition, pharmacokinetics and pharmacodynamic studies in pediatric population has not been adequately studied. Safety and efficacy of this drug in pregnant and lactating mothers has not yet been studied.

Sponsor has not conducted studies on drug metabolism in human. Metabolism studies are not generally performed on proteins which are degraded in to aminoacids which in turn are recycled in to other proteins. In addition, evaluation of drug-drug interaction has not yet been performed. Assessment of QT interval has not been studied in the clinical trials and should be studied according to the ICH E14 guidance.

7.2.1 Description of Patient Exposure

The study drug exposure for a subject was the number of weeks from the first dose of study drug to the last dose. Exposure summaries are provided below in table 15.

Table 15: Exposure of study subjects in controlled studies (phase 3 ITP safety set) and in the Comprehensive ITP Safety Set)

	Total Number of Subjects Exposed to Nplate (n)	Median Duration of Exposure (weeks)	Median/Mean Cumulative Dose (μg)	Median /Mean Number of Doses received	Average Median/Mean Weekly Dose (μg/kg/week)
Phase 3 ITP safety set (placebo-controlled studies)	84	24.00	4098.0/6302.4	23.0/21.3	2.48/3.30
Comprehensive ITP safety set[a]	271	37.10	8525/22443	33/46	3.31/4.40

a: Comprehensive ITP safety set: ITP safety set plus safety data from study 131.
Source: sponsors submission

Reviewer's comment: The duration of exposure in the two phase III placebo-controlled studies is only 24 weeks and the median duration of exposure in the entire chronic ITP safety database is approximately 37 weeks (~9 months). Patients in the comprehensive ITP safety set had higher median duration of exposure, median cumulative dose, and median number of doses, and average median weekly dose. A difference in the incidence rate of adverse events between phase 3 ITP controlled studies and comprehensive ITP safety set may be observed due to a difference in exposure parameters.

7.2.2 Dose Adjustment

In the controlled studies the protocol allowed dose adjustment based on weekly platelet count.

7.3 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 271 patients with chronic ITP were exposed to Nplate. The exposure data in the table below is based on the updated marketing application ITP safety set consisting of all subjects who received investigational product in an ITP study including data up to the data cutoff dates the 120-day safety analysis. A total of 271 patients received at least one dose of Nplate [in study 131, 52 patients received at least one dose of Nplate, and 29 patients received standard of care (SOC) treatment]; in 120-day Safety Update [Updated Marketing Application ITP Safety Set 219/229 received at least one dose of Nplate]

The demographic characteristic of patients enrolled in the trial including distribution by gender and race, age, weight and ethnic at baseline is presented in Table 16.

Table 16 : Demographic and Baseline Characteristics (Safety Analysis Set)

Patient Demographics	Marketing ITP Safety Set[a] (N=229)	Study 131 (N= 83)[b]
Age (yrs)		
n	229	83
Mean	51.3	54.3
SD	16.3	17.9
Median	52.0	55.0
Min, Max	1, 88	18,86
Sex - n (%)		
Female	149 (65.1)	44 (53.0)
Male	80 (34.9)	39(47.0)
Race - n (%)		
White or Caucasian	180 (78.6)	71 (85.5)
Black or African American	14 (6.1)	2 (2.4)
Hispanic or Latino	14 (6.1)	7 (8.4)
Asian	7 (3.1)	1 (1.2)
Japanese	12 (5.2)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	1 (1.2)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0 (0.0)
Aborigine	0 (0.0)	0 (0.0)
Other	1 (0.4)	1 (1.2)
Baseline Weight (kg)		
n	228	80
Mean	83.2	84.6
SD	24.2	20.6
Median	78.1	85.0
Q1, Q3	65.5, 96.2	73.0, 96.
Min, Max	44, 176	46, 162

Source: Sponsors Submission

a: The marketing ITP safety set includes all ITP patients except patients in study 131. A total of 219 out of 229 ITP patients received at least one dose of Nplate.

b: Study 131 is an ongoing, open label, multicenter, randomized (2:1), SOC-controlled, 52 week treatment study comparing Nplate with SOC in ITP patients. In this study, a total of 52 out of 83 enrolled ITP patients received at least one dose of Nplate.

Study 131 is an ongoing, phase 3b, multicenter, randomized, SOC-controlled, open-label, 52-week treatment study designed to compare Nplate and medical standard of care. The starting dose is 3 μg/kg, adjusted as needed to a maximum dose of 10 μg/kg in order to maintain platelet counts between 50 and 200 x 10^9/L. The safety analysis dataset includes 28 subjects in the SOC group and 51 subjects in the Nplate group.

Reviewer's comment: The demographic characteristics of patients exposed to Nplate in comprehensive ITP safety set was similar to those observed in the two phase 3 controlled studies.

7.4 Adverse Events

The table below summarizes the overall incidence of adverse events in the phase 3 controlled studies.

Table 17: Overall Summary of Adverse Events in Controlled Phase 3 Studies (Phase 3 ITP Safety Set)

	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

Reviewer's comment: The number of subjects reporting any adverse event was numerically higher in Nplate group compared to placebo. Both groups reported similar rate of severe adverse events. However, the number of subjects reporting life threatening adverse events was numerically higher in Nplate arm. Fatal adverse events were more common in placebo patients [3(7.3%) vs. 1 (1.2%)]. Overall the placebo arm showed a higher incidence of death compared to Nplate.

The following table shows the incidence of duration adjusted adverse events in the comprehensive ITP safety set.

Table 18: Overall Summary of Duration-Adjusted Adverse Event Incidence Rate in Comprehensive ITP Safety Set

	Comprehensive ITP Safety Set), Nplate([c]Pt-yr=276.9) N=271[a], n (r)
Number of Adverse Events Reported	4979 (1797.9)
Number of Adverse Events Reported with Severity of	
Severe	278 (100.4)
Life-threatening	32 (11.6)
Fatal	8 (2.9)
Number of Serious Adverse Events Reported[b]	212 (76.6)
Number of Treatment-Related Adverse Events Reported	556 (200.8)
Number of Treatment-Related Adverse Events Reported with Severity of	
Severe	40 (14.4)
Life-threatening	7 (2.5)
Fatal	2 (0.7)
Number of Treatment-Related Serious Adverse Events Reported	38 (13.7)
Number of Adverse Events leading to study withdrawal	19 (6.9)

[a] N = number of subjects who received at least one dose of investigational product over the course of all ITP studies.
[b] Serious adverse event includes any event that is fatal, life-threatening (places subject at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other significant medical hazard.
[c] Pt-yr = Total subject years on study. n = Number of adverse events. r = Study duration adjusted event rate per 100 subject-years (n / Pt-yr * 100).

Multiple occurrences of the same non-fatal event for a subject are counted as separate events. Multiple fatal adverse events for the same subject were counted once.

Reviewer's comment; There were 3 deaths that were newly identified during the 120-day reporting period (aplastic anemia in subject 90502 (Study 20040209); superficial thrombophlebitis in subject 91701 (Study 20040209); and intestinal infarction in subject 92501 (Study 20040209)). The fatal event of superficial thrombophlebitis in subject 91701 was reported in error; the sponsor confirmed

from the site that the subject did not die of this reported event, but instead died approximately 3 months after study discontinuation of a bleeding event related to ITP.

The study duration-adjusted event rate (events/100 subject-years on study) for fatal adverse events during an ITP study was comparable for Nplate-treated subjects in the 120-day analysis (2.9).

7.4.1 Deaths

The incidence of death in the two pivotal studies and comprehensive ITP safety set are summarized below.

7.4.2 Deaths in the Two Pivotal Studies

In the two pivotal studies, fatality rate for the Nplate group was lower than that for the placebo group (1% vs. 7%). The single death in the Nplate group was due to intracranial hemorrhage, a complication of ITP expected not to be exacerbated by Nplate therapy (see table 19).

Table 19: Fatal Adverse Events (Phase 3 studies)

Preferred Term	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)
Number of Subjects Reporting Fatal Adverse Events	3 (7.3)	1 (1.2)
Hemorrhage Intracranial	0 (0)	1 (1.2)
Cerebral Hemorrhage	1 (2.4)	0 (0)
Pneumonia Primary Atypical	1 (2.4)	0 (0)
Pulmonary Embolism	1 (2.4)	0 (0)

Source: sponsors submission

Reviewer's comment: Overall the placebo arm showed a higher incidence of death compared to Nplate. However, the one case of death in Nplate arm was associated with post-cessation thrombocytopenia and subsequent intracranial hemorrhage. A conclusion can not be made based on the drug-relatedness.

7.4.3 Total Number of Deaths in Comprehensive ITP Safety Set

Demographic characteristics of subjects and the cause of death are shown below:

Table 20: Fatal Adverse Events (Comprehensive ITP Safety Set)

	Phase 3 Controlled Trials		Comprehensive ITP Safety Set
	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)	Nplate (N = 271) n (%)
Number of Subjects Reporting Fatal Adverse Events	3(7.0)	1(1.2)	8(3.0)
Pneumonia primary 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)
Superficial Thrombophlebitis	0	0	1(0.4)
Intestinal infarction	0	0	1(0.4)
Acute respiratory distress syndrome	0	0	1(0.4)

Reviewer's comment: Fatal adverse events were more common in placebo patients compared to Nplate group [3(7.0%) vs. 8(3.0%)]. When the data from the pivotal studies are pooled with other uncontrolled ITP studies in the Nplate development program, the fatality rate for the Nplate group increased from 1.2% (pivotal studies) to 3.0% (all studies) but remained well below a placebo rate of 7.0% (all studies).

In the Nplate arm, an 80 year old man died after he received six months of Nplate and experienced a thrombotic cerebrovascular accident three days after discontinuation of the drug, followed by thrombocytopenia and intracranial hemorrhage. In the placebo arm, there were three patients who died of pneumonia, pulmonary embolism, and cerebral hemorrhage, respectively.

7.4.4 Serious Adverse Events

7.4.5 Serious Adverse Events (Phase 3 ITP Safety Set)

The serious adverse events in the phase 3 controlled studies compared to placebo are summarized below.

Table 21: Serious Adverse Events (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)
Number of Subjects Reporting Serious Adverse Events	8 (19.5)	14 (16.7)
Gastrointestinal Hemorrhage	0 (0)	2 (2.4)
Platelet Count Decreased	2 (4.9)	2 (2.4)
Hemorrhage Intracranial	1 (2.4)	1 (1.2)
Angioneurotic Edema	0 (0)	1 (1.2)
Appendicitis	0 (0)	1 (1.2)
B-Cell Lymphoma	0 (0)	1 (1.2)
Bone Marrow Disorder	0 (0)	1 (1.2)
Cerebrovascular Accident	0 (0)	1 (1.2)
Ecchymosis	0 (0)	1 (1.2)
Epistaxis	0 (0)	1 (1.2)
Haematochezia	0 (0)	1 (1.2)
Head Injury	0 (0)	1 (1.2)
Hypersensitivity	0 (0)	1 (1.2)
Hypertension	0 (0)	1 (1.2)
Hypovolaemia	0 (0)	1 (1.2)
ITP	0 (0)	1 (1.2)
Oral Mucosal Petechiae	0 (0)	1 (1.2)
Pericardial Effusion	0 (0)	1 (1.2)
Peripheral Embolism	0 (0)	1 (1.2)
Peripheral Ischemia	0 (0)	1 (1.2)
Road Traffic Accident	0 (0)	1 (1.2)
Sternal Fracture	0 (0)	1 (1.2)
Suicide Attempt	0 (0)	1 (1.2)
Pneumonia	2 (4.9)	0 (0)
Anemia Hemolytic Autoimmune	1 (2.4)	0 (0)
Cerebral Hemorrhage	1 (2.4)	0 (0)
Evan's Syndrome	1 (2.4)	0 (0)
Gastric Hemorrhage	1 (2.4)	0 (0)
Headache	1 (2.4)	0 (0)
Petechiae	1 (2.4)	0 (0)
Pneumonia Primary Atypical	1 (2.4)	0 (0)
Pulmonary Embolism	1 (2.4)	0 (0)
Purpura	1 (2.4)	0 (0)

Reviewer's comment: Rates of serious adverse events were not appreciably different between placebo and Nplate groups (20% placebo vs. 17% Nplate).

7.4.6 Dropouts and/or Discontinuations

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

Table 22: Incidence of Dropouts and/or Discontinuations in the controlled phase 3 studies

	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

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

For narratives of these patients please refer to appendix.

The adverse events leading to dropouts and/or discontinuations in the comprehensive ITP safety set are summarized in the table below:

Table 23: Adverse Events Leading To Dropouts and/or Discontinuation in Comprehensive ITP Safety Set

Study	PID	Age (years)/ Sex	Dose	AE Leading to Withdrawal / Severity
20030105	1231	40 / M	Nplate	Bone marrow disorder/ severe
20030212	351	62 / F	Placebo	Metastases to liver / severe
20030212	1958	48 / F	Nplate	B-cell lymphoma / life threatening
20030213	300123	27 / F	Nplate	Vaginal hemorrhage / severe*
20030213	300331	60 / F	Nplate	Bone marrow disorder / severe
20030213	301202	30 / M	Nplate	Myelofibrosis / moderate
20030213	301603	44 / F	Nplate	Musculoskeletal pain / moderate Headache / mild
20030213	301923	44 / F	Nplate	Deep vein thrombosis / moderate
20030213	310230	56 / F	Nplate	Thrombophlebitis septic / severe
20030213	310832	56 / M	Nplate	Multiple myeloma / life threatening
20040209	91701	66 / F	Nplate	Thrombophlebitis superficial / fatalb
20040209	92501	72 / F	Nplate	Portal vein thrombosis / severec
20040209	902002	52 / F	Nplate	Pulmonary embolism / life threatening Deep vein thrombosis / life threatening
20060131	131210071	54 / F	Nplate	Pulmonary embolism / moderate

* The patient with vaginal hemorrhage was identified as having bone marrow disorder also.
1 these 3 patients have been in controlled studies (see table23)

Reviewer's comment: The major causes of study withdrawal are thromboembolic events and bone marrow disorders. Since the majority of these cases were from uncontrolled studies, a definitive conclusion may not be made at this time.

7.4.7 Specific Primary Safety Concerns

The following table shows the incidence of adverse events of special interest in patients exposed to Nplate in the comprehensive ITP safety set.

Table 24: Incidence of the adverse events of special interest in patients exposed to Nplate compared to placebo in the comprehensive ITP safety set and controlled phase 3 studies.

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

Reviewer's comment: Overall, in the comprehensive ITP safety set, there was a higher incidence of thrombotic/thromboembolic adverse events and bone marrow abnormalities in the ITP patients compared to placebo patients. Also incidence rates of these two events increased with long term exposures.

Although, the incidence of neoplasm was lower in the Nplate patients compared to placebo, the rate increased with the long term exposure to Nplate.

A difference in the incidence rate of the above adverse events between phase 3 ITP controlled studies and comprehensive ITP safety set may be observed due to a difference in exposure parameters (see Table 15) and/or other variables that were unaccounted in the uncontrolled studies.

7.4.7.1 Serious Bleeding Events (controlled studies)

Serious bleeding events for the controlled phase 3 ITP safety set are summarized in the table below.

Table 25: Serious Bleeding Events (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)
Subjects reporting serious bleeding adverse events of interest	4 (9.8)	5 (6.0)
Gastrointestinal Hemorrhage	0 (0)	2 (2.4)
Hemorrhage Intracranial	1 (2.4)	1 (1.2)
Ecchymosis	0 (0)	1 (1.2)
Epistaxis	0 (0)	1 (1.2)
Haematochezia	0 (0)	1 (1.2)
Oral Mucosal Petechiae	0 (0)	1 (1.2)
Cerebral Hemorrhage	1 (2.4)	0 (0)
Gastric Hemorrhage	1 (2.4)	0 (0)
Petechiae	1 (2.4)	0 (0)
Purpura	1 (2.4)	0 (0)

Source: Sponsors report

Reviewer's comment: The rate of serious bleeding events was numerically lower for the Nplate group than for the placebo group. However, a definitive conclusion cannot be made because the study population was small.

7.4.7.2 Bone Marrow Abnormalities in Controlled and Comprehensive Data Set

Bone marrow abnormalities were reported in 10 out of 271 patients exposed to Nplate in comprehensive ITP safety set. There were no bone marrow abnormalities in the placebo group.

Table 26 demonstrates the bone marrow abnormalities in six of the ten ITP patients. The remaining patients are described in the Narratives.

Table 26: Summary of Patients with Increased Reticulin in Bone Marrow

Age, Race, Sex	Platelet Range x 10^9/L	BM baseline	BM Post -Nplate	Dose & Duration
40 WM	5 - 10	Patchy, mild reticulin, generalized hypoplasia	Diffuse, mod-severe reticulin fibrosis,meg,myeloid,hyperplasia ↑ dyspoietic megakaryocytes	1-9 ug/kg 5 w/doses
31 WM	27- 523 19-93	not given	Hypercellular BM, Moderate -severe reticulin	1-18 ug/kg 24 w/doses
53 WM	6- 88	Negative	Negative, central pathology Positive, local pathology	1-5ug/kg, 24wks/doses 5-8ug/kg 44 w/doses
58 BM	7 - 69 7 -33	Mild reticulin (0-1+)	moderate reticulin fibrosis (2 bone marrow exams: during study 105 and 213)	1-15ug/kg, 24w/doses 15ug/kg, 37w/doses
55 WF	12- 71 22 - 54 ↓ to 3	Not given	Mod- severe reticulin fibrosis	1-9ug/kg, 24 w/doses[3] 9-13ug/kg, 3 w/doses
37 WM	5 - 12	interstitial lymphocytosis No notes regarding reticulin found	Significant reticulin fibrosis, dyserythropoiesis, dysmegakaryopoiesis	1-9 ug/kg 24 w 7-?ug/kg 2or3wks/doses

Reviewer's comment: Animal studies have shown reticulin fibrosis in the bone marrow which was reversible upon discontinuation of Nplate. Also investigators suggest that there is a relationship between increase in marrow content of transforming growth factor beta and reticulin fibrosis. These studies suggest that TPO molecule stimulates megakaryocytes to produce TGF beta, which in turn, results in reticulin formation. Nplate administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow.

Bone marrow abnormalities were reported in 10 out of 271 patients exposed to Nplate in comprehensive ITP safety set. Nplate was discontinued in 4 of the 271 patients because of bone marrow reticulin deposition. Six additional patients had increased reticulin deposition observed upon bone marrow biopsy. Most patients had nucleated RBC in peripheral blood.

All 10 patients with bone marrow 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. One patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate therapy (see Narrative for patient # 311131). Clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias with Nplate.

The stimulation of megakaryocytic proliferation in the bone marrow as an effect of Nplate can be a possible explanation for this adverse event. Bone marrow reticulin fibrosis is an important safety concern to consider for long term treatment with Nplate, especially in patients receiving high doses of the drug (doses >5 mcg/kg/week). Although minimal (grade 0-1) reticulin can be found rarely in the bone marrow of normal individuals and in various benign conditions, excess deposition of reticulin (grades 2-4), an increase severity of marrow reticulin formation compared to the baseline, and presence of collagen deposition (myelofibrosis) could be of serious concern in patients treated with Nplate. Reticulin fibrosis is generally identified with silver stain whereas collagen fibrosis is identified with trichrome stain. Reticulin fibrosis is potentially a reversible process, whereas collagen fibrosis is less likely to be reversible and could be associated with myelofibrosis and pancytopenia.

7.4.7.3 Thrombotic/Thromboembolic Events (controlled and comprehensive studies)

The incidence of thrombotic/thromboembolic events is presented in table 27.

Table 27: Incidence of Thrombotic/Thromboembolic Events in Phase 3 Controlled and Comprehensive ITP Safety Set

	Phase 3 Controlled Trials		Comprehensive ITP Safety Set
	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)	Nplate (N = 271) n (%)
Subjects Reporting Thrombotic/Thromboembolic	1 (2.4)	2 (2.4)	15 (5.5)
Deep Vein Thrombosis	0(0)	0 (0)	1 (0.36)
Pulmonary Embolism	1 (2.4)	0 (0)	3 (1.1)
Portal Vein Thrombosis	0(0)	0 (0)	2 (0.7)
Thrombophlebitis Superficial	0(0)	0 (0)	1 (0.36)
Thrombosis	0(0)	1 (1.2)	2 (0.7)
Acute Myocardial Infarction	0(0)	0 (0)	2 (0.7)
Cerebrovascular Accident	0(0)	1 (1.2)	1 (0.36)
Coronary Artery Occlusion	0(0)	0 (0)	1 (0.36)
Intestinal Infarction	0(0)	0 (0)	0 (0)
Transverse sinus thrombosis	0 (0)	0 (0)	1 (0.36)
Peripheral Embolism	0 (0)	0 (0)	1 (0.36)

Reviewer's comment: compared to placebo patients, Nplate-exposed patients showed a higher incidence of thromboembolic events(2.4% vs. 5.5%) in the comprehensive ITP safety set, however in the controlled studies there was no difference between placebo and Nplate arm(see table 24).

This data from comprehensive ITP safety set suggests that Nplate might be associated with increased rate of thrombotic/thromboembolic events. However, the above incidence rate has not been adjusted for the duration of exposure.

7.4.7.4 Immunogenicity

The incidence of immunogencity for healthy individuals and ITP patient populations receiving Nplate was assessed and compared (see Table 28 and table 29).

Table 28 : Immunogenicity data from healthy subjects and ITP patients receiving Nplate

	Preexisting anti- Nplate Ab	Pre-existing anti- TPO Ab	Developing anti- Nplate Ab	Developing anti- TPO Ab	Neutralizing anti-Nplate Ab	Neutralizing anti-TPO Ab
Healthy volunteers (n=78)	2/78 (3.6%)	3/78 (5.4%)	1/78 (1.8%)	1/78 (1.8%)	0/78 (0%)	0/78 (0%)
ITP patients, Nplate (n=204)	17/204 (8.3%)	13/204 (6.4%)	17/204 (8.3%)	10/204 (4.9%)	1/204 (0.5%)	0/204 (0%)

Reviewer's comment: Some ITP patients in the Nplate group had pre-existing antibodies to Nplate and eTPO. These pre-existing antibodies to Nplate might be due to autoimmune nature of the disease. Whether or not these antibodies affect the development of post dose antibody to Nplate or eTPO is not clear.

Table 29: Incidence of Development of Binding and Neutralizing Antibodies in ITP subjects tested

	ITP subjects tested n = 225 (%)
Binding Antibodies	
Nplate	23 (10)
TPO	12 (5)
Neutralizing Antibodies	
Nplate	1 (0.44)
TPO	0 (0)

Reviewer's comment: The rate of development of neutralizing antibodies was low in ITP subjects tested. The impact of antibody development on the efficacy and safety of Nplate is currently unknown. It would be essential 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. (See section 1.4).

7.4.7.5 Neoplasms

The incidence of Neoplasms in the controlled phase 3 studies and comprehensive ITP safety set are summarized in the tables below:

Table 30: Incidence of Neoplasms in the Controlled Phase 3 studies (phase 3 ITP Safety Set)

Preferred Term	Phase 3 Controlled Trials		Comprehensive ITP Safety Set
	Placebo (N = 41) n (%)	Nplate (N = 84) n (%)	Nplate (N =271) n (%)
Subjects reporting neoplasm adverse events of interest	5 (12.2)	2 (2.4)	20 (7.3)
B-Cell Lymphoma	0 (0)	1 (1.2)	1(0.4)
Basal Cell Carcinoma	0 (0)	1 (1.2)	3(1.1)
Benign Ovarian Tumor	1 (2.4)	0 (0)	0
Fibroma	1 (2.4)	0 (0)	0
Lung Neoplasm	1 (2.4)	0 (0)	3(1.1)
Metastases to Liver	1 (2.4)	0 (0)	0
Multiple Myeloma	1 (2.4)	0 (0)	1(0.4)
Uterine Leiomyoma	1 (2.4)	0 (0)	0
Hepatic Neoplasm	0	0	2(0.7)
Axillary Mass	0	0	1(0.4)
Breast Masses	0	0	3(1.1)
Uterine Polyp	0	0	1(0.4)
Colon Cancer	0	0	1(0.4)
Laryngeal Neoplasm	0	0	1(0.4)
Thyroid Mass	0	0	1(0.4)
Malignant Melanoma	0	0	1(0.4)
Polyp	0	0	1(0.4)

The incidence of neoplasm was lower in Nplate patients compared to the placebo patients in the phase 3 controlled studies (12% versus 2.4%). The incidence rate of neoplasm in comprehensive ITP safety set was 20 (7.3%) (see table 24).

7.4.7.6 Post-cessation Thrombocytopenia:

The summary of cases with post-cessation thrombocytopenia from early and controlled clinical studies is presented below:

Table 31 : Summary of Patients with post-cessation thrombocytopenia

Subject ID	Preferred Term
1605	Thrombocytopenia
522	Thrombocytopenia
1624	Thrombocytopenia
10203	Thrombocytopenia
6051	Intracranial hemorrhage

Within the early clinical studies, 4/57 patients developed thrombocytopenia after discontinuation of Nplate. The degree of thrombocytopenia was below the pre-treatment levels. Two of these patients developed thrombocytopenia after only a single dose of Nplate (one after 4.5 weeks of receiving a dose of 10 mcg/kg and another patient 2 weeks after receiving a single dose of 300 mcg Nplate). The other two patients developed thrombocytopenia within 2 and 3 weeks after the 4th and 6th doses respectively. In all cases platelet counts returned to baseline levels within approximately 2 weeks after the onset and some required treatment.

In the controlled phase 3 studies, one death was reported in the Nplate arm. The death occurred in an 80 year old man who developed thrombotic cerebrovascular accident 3 days after cessation of Nplate and died of intracranial hemorrhage a week later. His platelet count after discontinuation on Nplate dropped from 107 x 10^9/L to 5x 10^9/L.

Reviewer's comment: One of the possible mechanisms for post-cessation thrombocytopenia might be the suppression of circulating endogenous TPO with the use of Nplate. Post-cessation thrombocytopenia could be of concern in particular in patients who may discontinue Nplate abruptly and are not taking other concomitant medications for ITP.

7.4.8 Summary of Common Adverse Events

The common adverse events are summarized in Table 32.

Table 32 : Incidence of Adverse Events ≥ 5% Nplate or Placebo Group by Preferred Term in Descending Order of Frequency

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)
Upper Respiratory Tract	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

Reviewer's comment: 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 between Nplate and placebo.

7.4.9 Special Animal and/or In Vitro Testing

In vitro studies have shown that Nplate has clear binding affinity to c-Mpl derived from several species.

Non human primates were less sensitive than rodents to the pharmacodynamic effects of Nplate. Bone marrow fibrosis was diagnosed only by H&E staining. No special stains were performed. This adverse event was reversible upon discontinuation of Nplate. Repeat dose studies in rats showed deaths in all groups exposed to Nplate, more frequently in the 100 mcg/kg group.

Femoral and sternal bone hyperosteosis and myelofibrosis were observed in surviving rats at the end of the treatment with a reversible histology after recovery. More than half of the surviving rats were positive for anti- Nplate antibodies. Most of these antibodies had neutralizing activity against the drug with decreased biological response to Nplate. However, thrombocytopenia did not occur in the antibody positive rats.

Embryo-fetal studies in mice showed increase post-implantation loss, and reduction in maternal body weight. In rats at doses 10 fold higher than the highest anticipated clinical dose, there was a slight increase in pup mortality. Nplate showed no effect on fertility or reproductive performance and was not an embryo-fetal toxicant in rats, or rabbits at clinically relevant doses.

Reviewer's comment: Sponsor has used adequate animal models to explore potential adverse events such as reticulin deposition in the bone marrow. QT studies were not performed in animal models.

7.4.10 Metabolic, Clearance, and Interaction Workup

No studies on metabolic/ transporter pathways have been performed in human or animal. Classical biotransformation studies as performed for pharmaceuticals are not needed in proteins.
Since Nplate is an Fc fusion protein, it's suggested that this drug is degraded into amino acids and then recycled into other proteins.

No studies in patients with renal or hepatic impairment and geriatric patients have been conducted. Number of healthy or ITP patients has not been sufficient enough at each dose level for assessing the effect of demographic factors such as sex, age, and body weight on Nplate exposure. However, based on the limited available data, age or gender does not appear to have an effect on the primary efficacy endpoint, durable platelet response. Although fixed doses demonstrated a dose response in peak platelet counts after the first dose, the peak platelet count appeared to be lower for subjects who had higher body weight than those who had lower body weight, suggesting that weight-based dosing be a more appropriate dosing strategy to provide treatment for subjects with ITP.

There has not been an in vitro analysis to study drug-drug interaction, since P450 enzyme system is not expected to play any role in Nplate biotransformation.

7.4.11 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

There have been two other recombinant TPOs which have undergone extensive clinical testing. These two include human TPO(rHuTPO) (with identical aminoacid sequence to eTPO) and pegylated recombinant megakaryocyte growth and development factor (PEG-rHuMGDF), a non-glycosylated molecule that contains the first 163 amino acids of eTPO. Both are potent stimulators of platelet production in human.

PEG-rHuMGDF was associated with persistent thrombocytopenia in 13 of 325 healthy individuals who received 2-3 doses. Production of neutralizing antibodies to PEG-rHuMGDF with cross reactivity and neutralizing antibodies to eTPO and subsequent thrombocytopenias was one of the major safety concerns of this drug class (*Thrombocytopenia caused by the development of antibodies to thrombopoietin, Junzhi L. et. al. Blood, 2001.volume 98, Number 12*).

7.4.12 Laboratory Findings

Hematology:
Hematologic parameters such as hematocrit, hemoglobin, MCV, MCH, MCHC, NRBC, RBC, red cell distribution width, and WBC were similar in both placebo and Nplate patients.

Serum Chemistry:
In controlled phase 3 studies, by week 25, median LDH in Nplate arm was increased by 10.5 U/L compared to 5.5 U/L decrease in LDH in placebo arm. There was one a 45 year old woman with ITP (patient # 10302) who had moderate to severe increase in LDH 9 days into the study (see narrative).

7.4.13 Vital Signs

In phase 3 ITP controlled studies, baseline and week 25 results for all vital sign parameters were similar between the two groups. There were no clinically significant differences in the incidence of vital sign changes between Nplate and placebo groups.

7.4.14 Electrocardiograms (ECGs)

No QTc studies have been performed in human. Since the sponsor has not performed QTc evaluations, this study will be part of the post marketing requirements.

7.4.15 Human Carcinogenicity

No adequate and well controlled studies in human have been performed to address this issue.

7.4.16 Withdrawal Phenomena and/or Abuse Potential

The sponsor has not performed any study to evaluate withdrawal phenomena and/or abuse potential.

7.4.17 Special Safety Studies

No special safety studies have been conducted.

7.4.18 Drug-Drug Interactions

No studies have been conducted to assess the interaction of Nplate with specific drugs.

During the placebo controlled studies patients were allowed to receive concomitant medications corticosteroids, azathioprine, or danazol.

7.4.19 Human Carcinogenicity

The carcinogenic potential of Nplate has not been evaluated. The mutagenic potential of Nplate has not been evaluated. Nplate had no effect on the fertility of rats at doses up to 10 times the maximum recommended human dose.

7.4.20 Human Reproduction, Pregnancy Data, Nursing

It is not known whether Nplate crosses the placenta or is excreted in milk in humans. The risk-benefit ratio of Nplate administration during pregnancy and lactation has not been established, since no adequate and well-controlled studies in this specific group of patients have been performed.

In animal reproduction and developmental toxicity studies, Nplate crossed the placenta, and adverse fetal effects included thrombocytosis, post-implantation loss and an increase in pup mortality.

In rat and rabbit developmental toxicity studies at Nplate doses ranging from 1 to 10 times the maximum recommended human dose (MRHD) no evidence of fetal harm was observed. In mice at doses 10 times the MRHD, reductions in maternal body weight and increased post-implantation loss occurred. In a prenatal and postnatal development study in rats, at doses 10 times the MRHD there was an increase in peri-natal pup mortality. Nplate crossed the placental barrier in rats and increased platelet counts at clinically equivalent and higher doses.

Because many drugs are excreted into human milk and because of the potential for serious adverse reactions in nursing infants from Nplate, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the known benefits of breastfeeding.

7.4.21 Overdose Experience

There has been a case of overdose reported. The case was a 34 year old African American woman) (patient # 300321 in study 213) whose baseline platelet count was 1k. Patient was allowed to self-inject Nplate on week 85, 86, and 87. The patient injected 5 mcg/kg/wk for 3 consecutive weeks instead of 3 mcg/kg, and her platelet count subsequently increased to >1 million at weeks 88 and 89. After Nplate was withheld, the platelet count got dropped to 3k.

Medical Reviewer's comment: The above overdose experience suggests that patients and health care providers require education about Nplate and appropriate use of the product (see Post Marketing Recommendation).

7.4.22 Pediatric and Effect on Growth

The safety and effectiveness in pediatric patients (< 18 years) have not been established.

7.5 Additional Submissions

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

8 Postmarketing Experience

The product is not approved in any country.

9 Overall Assessment

The reviewed studies demonstrated safety and efficacy of Nplate for treatment of adult patients with ITP who are refractory to low-dose corticosteroids or splenectomy.

The most common adverse reactions (≥ 5% higher patient incidence in Nplate versus placebo) arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia. Headache was the most commonly reported adverse reaction that did not occur at ≥ 5% higher patient incidence in Nplate versus placebo.

Nplate administration increases the risk for development or progression of reticulin fiber deposition, thromboembolic events, post-cessation thrombocytopenia and immunogenicity.

Nplate appears to be 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).

10 Appendices

10.1 Literature Review/References

The electronic copies of literature references were submitted. The references are included in the appendix:

10.2 Labeling Recommendations

Electronic copies of the labeling proposal for Nplate were submitted by the sponsor. The proposed labeling recommendations have been approved after several changes have been made.

10.3 Advisory Committee Meeting

Following the March 12, 2008, Oncologic Drugs Advisory Committee (ODAC) meeting, the committee unanimously voted to recommend approval of Nplate for adult patients with chronic ITP refractory to corticosteroids or splenectomy.

10.4 Narratives

10.4.1 Narratives of patients with bone marrow disorder

Patient 1231:
This patient was in study 20030105, was treated with Nplate for 5 weeks. Patient was a 40 year old Caucasian man, whose bone marrow fibrosis was diagnosed, 4 months before entering the study. He had a baseline nucleated RBC (NRBC) ranging between 1-5 per 100. WBC with a red cell distribution width (RDW) of 22.5% and platelet count of 5 x 10^9/L. Baseline bone marrow biopsy and aspirate (4 months before study entry) showed generalized marrow hypoplasia and mild patchy increase in reticulin. He received 5 weekly doses of Nplate with doses ranging between 1-9 ug/kg. His maximum platelet count during the study was 10 x 10^9 /L. Patient was withdrawn from the study on week 7, due to increase number of NRBCs to 47 per 100 WBC on week 6 of study. Platelet count on that day was 5 x 10^9 / L. Result of bone marrow aspirate/biopsy obtained at the time of discontinuation (week 7) showed moderately hypercellular bone marrow, with myeloid and megakaryocytic hyperplasia, and increased dyspoietic megakaryocytes. This bone marrow biopsy showed a significant worsening of the degree of reticulin fibrosis from patchy mild at the baseline to diffuse, moderate to severe reticulin fibrosis, with no evidence of neoplastic lymphoproliferative disorder. At this time the number of NRBC had increased to 93 per 100. Masson trichrome stain of bone marrow was negative for collagen. A follow up BM assessment (3 months later) showed significant reduction in megakaryocytic/hyperplasia/dyspoiesis, as well as a return to mild, patchy reticulin fibrosis, which was present at baseline. Therefore this reversible increase in reticulin fibrosis could have strongly been associated with Nplate exposure.

Patient 301202:
31 year old Caucasian splenectomized male, who had received Nplate in Study 20000137 part A (10 ug/kg on days 1 and 22). Baseline platelet count was 27 x 10^9 /L, peaked to 523 x 10 /L during the study. No BM- related incidents were reported at that time.

About 10 months after completing study 2000137, he enrolled in study 20030213 with a baseline platelet count of 19 x 10^9 / L. He received weekly Nplate for 22 weeks with doses between 1- 18 ug/kg. Platelet counts ranged from 12 x 10^9 / L to 93 x 10^9/ L. NRBCs were increased (numbers are not given) at weeks 15 and 22 measurements. There was increasing number of blasts in peripheral blood from 1% at week 20 to 6% at week 22. BM aspirate at week 22 showed hypercellularity with trilineage hematopoiesis, megakaryocytic hyperplasia, and no evidence of leukemia (% blasts is not given). This BM biopsy showed moderate (with patchy areas of dense severe) increase in reticulin. Trichrome stain was not significant for mature collagenous fibrosis. This was reported as a serious, treatment- related adverse event and Nplate was discontinued at week 24. Patient remained on the study for safety

observation until week 59. Additional bone marrow exams at weeks 33 and 46 showed mild diffuse reticulin fibrosis, suggesting the reversibility of this process, with no evidence of acute leukemia. Week 46 bone marrow biopsy didn't show changes compared to week 33. Patient was discontinued from the study on week 59. Based on the follow up result and decrease in the degree of reticulin fibrosis, investigator changed the term myelofibrosis to increased reticulin, due to negativity of trichrome stain and positivity of reticulin stain. Because of improvement of marrow picture with discontinuation of the Nplate, the case was inconsistent with a clonal disorder of chronic idiopathic myelofibrosis (CIMF) or agnogenic myeloid metaplasia.

Patient 303231:
This 53 year old Caucasian male with ITP, relevant history included splenectomy, bleeding episodes, hypertension, gammopathy and alcoholism. During study 20030105, he received doses of AMG between 1-5 ug/kg over 24 weeks and reached a durable platelet response. After completion of the previous study, he immediately enrolled in to study 20030213, with baseline platelet of 6 x 10^9 /L. Doses of Nplate were between 5-8 ug/kg up to the data cut off date (week 44). Platelet count (pretty stable) ranged between 45 - 88 x 10^9 /L.
Since he was enrolled in study 20030123 (ancillary study to evaluate bone marrow), his bone marrow biopsy at week 12 showed mild reticulin fibrosis (based on a local reading), but not observed by the pathologist who reviewed the biopsy for study 20030123, nor was noted at baseline before study 20030105. This patient continued to be on study 213.

Patient 303630:
This patient who participated in study 20030105 and 20030213(ongoing) is a 58 year old African American man with history of splenectomy, received Nplate with doses ranging between 1-15 ug/kg over a period of 24 weeks. Baseline bone marrow assessment (2 years prior to this study had shown mild reticulin fibrosis (grade 0-1). Baseline platelet count was 7 x 10^9 / L and no NRBCs in peripheral blood smear. On week 14 of the same study(Nplate dose of 14 ug/kg), there was increase in NRBCs(47 per 100 WBC) and bone marrow exam on the same day showed markedly hypercellular marrow with granulocytic and megakaryocytic hyperplasia, and mild to moderate reticulin fibrosis (grade 1-2 on the scale of 0- 4). Platelet count at week 14 was 58 x 10^9 /L.

Patient was enrolled and started study 20030213 after 5 weeks of completion of 20030105. Starting dose was 15 ug/kg with baseline platelet of 7 x 10^9 / L and NRBC of 1 per 100 WBC. By week 8, staying on the same dose, platelet raised to 33 x 10^9/L, and NRBC peaked at 15 per 100 WBC. At this week bone marrow exam showed moderate reticulin fibrosis, with the same cellularity as week 14 of study 20030105. Nplate was withheld. Dexamethasoe (4 day course of pulse therapy) and mycophenolate mofetil were started, which kept platelet count at 22 x 10^9 / L. At week 23, Nplate was resumed at 15 ug/kg until week 52 (data cut off for this patient). Platelet counts from week 23 - 52 ranged between 9 to 42 x 10^9 / L except for on occasion of 204 x 10^9 /L at week 51 after dexamethasone addition to the Nplate, as rescue medication at week 50. The latest update by the sponsor indicates

that this patient is currently under three medications for ITP: Nplate (dose tapered to 8 ug/kg) + Dexamethasone (40 mg, every other week) + cellcept (1 gm, daily). No further bone marrow evaluation has been performed.

Patient 303851:
Study 20030213: thrombocytopenia started study day 25, Evan's syndrome started study day 50, bone marrow disorder started study day 53, study discontinued on study day 30 (consent was withdrawn).

This 55 year old Caucasian woman, (with history of SLE, HTN, no splenectomy) completed study 20030212 (24 weeks), she received doses of Nplate (1-9 ug/kg) with multiple missing doses due to non-compliance. Baseline platelets were 12 x 10^9 / L and during the study ranged between 3 and 71 x 10^9/ L. No bone marrow disorders were reported during this study (not sure if they performed a bone marrow exam at this time)

She started study 20030213 with baseline platelet count of 22 x 10^9 /L, starting dose of 9 ug/kg and increased to 13 ug/kg over 3 weeks. Platelet count peaked at 54 x 10^9 / L at week 2. On week 3(day 25), she developed severe thrombocytopenia and moderate ear hemorrhage, with a platelet count of 3 x 10^9 / L. After hospitalization, she received IVIG, corticosteroids and a platelet transfusion. Nplate was discontinued, platelet count increased to 14 x 10^9 / L on the same day. The day after her discharge she withdrew her consent from the study. Patient was re-hospitalized after 3 weeks with diagnosis of Evan's syndrome (anemia: hemoglobin: 6 g/dL, reticulocyte count: 12.8% and low plate let count of 4 x 10^9 / L). She received the following treatments for Evan's syndrome: IVIG, corticosteroids, and blood transfusion. Her hemoglobin rose to 11 g/dL after 4 days. Her platelet count increased to 78 x 10^9/ L. She underwent splenectomy on hospital day 9, and platelet count stabilized for a few days and again dropped to 18 x 10^9 / L soon after the splenectomy. With IVIG, her platelet count rose to 75 x 10^9/ L. She was discharged with her symptoms resolving on hospital day 13. Results of BM aspirate and biopsy during the last hospitalization showed diffuse, moderate to severe (grade 2-3) reticulin fibrosis. Trichrome stain was negative for collagen. Latest update after discontinuation from study 213 shows that her Evan's syndrome is in remission and no further bone marrow exams have been performed. In 2007, an MRI of brain showed mini clots in the brain (complaint of dizziness), after which she was placed on Coumadin for life time. She was diagnosed with antiphospholipid syndrome.

Patient 311131:
This 37 year old Caucasian man with history of splenectomy, hemolysis, asthenia and anemia, received Nplate weekly for a period of 24 weeks (study 20030105) with doses ranging from 1 to 9 ug/kg. Bone marrow biopsy was performed 5 days before the study 20030105 and showed interstitial lymphocytosis of slight intensity made majority by small mature lymphocytes with a reactive phenotype (positive CD3). No notes about reticulin fibrosis were found in sponsor's report. Evan's syndrome (thrombocytopenia, reported day 3 and hemolytic anemia, reported day 2 of study 20030213) was reported before the first administration of Nplate in study 20030213. About 3 weeks after completion of study

20030105, patient started Nplate (study 20030213) at a dose of 7 ug/kg, and a baseline platelet of 5 x 10^9 / L. Second (last?) it is not clear whether patient received another dose on day 15) dose was given on study day 8 and patient discontinued the study on day 23. Platelet counts were 4, 3, and 12 x 10^9/ L on study days 8, 15, and 22, respectively. Patient was hospitalized for thrombocytopenia (3 x 10^9 /L) with gingival bleeding, asthenia and dyspnea. He was treated with 2 units of platelet concentrates and methylprednisolone sodium succinate, which had no benefit. Patient was discharged home on prednisone, ferrous sulfate and vitamin B12, and folic acid. Result of bone marrow biopsy showed significant myelofibrosis (increased reticulin formation, with localized collagen deposition (positive Trichrome stain). No cytogenetic abnormality (i.e. Philadelphia chromosome and JAK2) were present. No clonal disorder was seen. Therefore this case was not consistent with a clonal myelofibrosis. A repeat bone marrow exam, which was done about 10 weeks after discontinuation of study showed the same diagnostic changes as the previous one. Following discontinuation of Nplate, anemia improved with corticosteroid therapy and platelet count increased (count is not given) and patient was reported to be improved (Evan's syndrome had resolved). As per Amgen's latest update on this patient: he is currently on prednisone (10mg) therapy. No recent bone marrow exams have been performed. The platelet count and hemoglobin is normal.

Patient #0331:
This 60 year old splenectomized woman with baseline platelet count of 9k, who received placebo in study 105(study1/splenectomized study) and after completion of that study, enrolled in study 213(study3/extension study) and received Nplate (dose range: 1-11mcg/kg/wk) for 47 weeks. On week 46 increased tear drop cells were noted in the peripheral blood smear and a bone marrow exam showed increased trilineage hematopoiesis suggestive of myeloproliferative disorder (essential thrombocythemia) versus proliferative phase of idiopathic myelofibrosis with increased reticulin formation. After discontinuation of Nplate, a follow up bone marrow exam showed stable reticulin fibrosis in bone marrow. In this patient baseline bone marrow examination was not given.

Patient # 90502:
This patient was a 75 year old white woman with history of diabetes mellitus, coronary artery disease, MI, hypertension, and breast cancer. Baseline platelet count was 33k and received 27 weekly doses of Nplate over 6 months (dose: 3-15 mcg/kg). She developed hypoglycemic shock, spinal fracture, and pneumococcal septicemia and superficial thrombophlebitis during the study. About 6 months into the study, she developed aplastic anemia with a marrow report of only focal erythropoiesis and myelopoiesis without convincing evidence of megakaryocytes, A peripheral blood smear at this time showed pancytopenia. A test for JAK2 point mutation was negative. The patient was also receiving multiple concomitant medications such as fenofibrate and carvedilol, which have been reported to cause cytopenias. This patient died 54 days after the diagnosis of aplastic anemia.

Patient # 300123:
A 27 year old splenectomized woman who initially received 5 doses of Nplate in study 137B. bone marrow exam was done one week after the 5th dose, reticulin was not described in the pathology report. After 8 months, she enrolled in study 213 and received Nplate with dose range of 1-10 mcg/kg for 36 weeks. She had a bone marrow exam week 18 of study 213 which showed megakaryocytic hyperplasia. No other abnormality was reported. Patient developed persistent vaginal bleeding with platelet of 15k for which Nplate dose was increased to 11mcg/kg. Subsequently peripheral blood smear showed increased NRBCs and a bone marrow exam showed increased (2+) reticulin, with a negative trichrome stain for collagen. Patient was hospitalized and Nplate was discontinued. A follow up bone marrow exam is not provided.

Patient # 1923:
A 44 year old lady on 6 weeks of Nplate (study 137B) with baseline platelet of 15k. After 10 weeks patient enrolled in study 213 and received 1-3 mcg/kg Nplate for 38 weeks. On week 38 she developed a severe anal fistula for which had a surgery. On week 118 she developed a portal vein thrombosis with abdominal pain for which was hospitalized and Nplate dose was increased to 4 mcg/kg and was treated with prednisone. Platelet count was very low (2k). A bone marrow exam showed mild reticulin and patient continued to received Nplate.

10.4.2 Deaths

Patient # 90502:
A 75 year-old white (Caucasian) woman with chronic refractory ITP, was enrolled into study 20040209. Her medical history was relevant for steroid-induced diabetes mellitus, coronary artery disease, myocardial infarction, anemia, hyperlipidaemia, hypertension and breast cancer. Baseline platelet count was 33 x 10^9/L. Patient received a total of 27 weekly doses of Nplate ranging from 3 µg/kg to 15 µg/kg. Platelet count values ranged from 5 to 155 x 10^9/L. During the study she developed hypoglycemia, pneumococcal septicemia, spinal fracture, superficial thrombophlebitis and eventually aplastic anemia. The bone marrow aplasia occurred about 6 months into study. Peripheral blood smear revealed severe thrombocytopenia, mild macrocytic normochromic anemia, and no circulating blasts. Bone marrow examination showed markedly hypocellular (5 to 10%) marrow approaching marrow aplasia, with only focal evidence of erythropoiesis and myelopoiesis, and convincing marrow megakaryocytes not identified, no increased marrow blast population seen, occasional minute reactive marrow lymphoid aggregate present, no granulomatous inflammation encountered, and no evidence of marrow involvement by primary or metastatic malignancy identified. Cytogenetic analysis for abnormal clones was negative. V617F JAK2 point mutation was negative. Nplate was held, however she died approximately 54 days after the onset of the event. A bone marrow/ peripheral smear from 5 years before the study was consistent with ITP.

Patient # 901001:
Patient is an 18 month old Asian girl who was diagnosed with ITP shortly after birth She participated in study 209(study in severely refractory ITP patients) for approximately 21 weeks (dose range: 3-13mcg/kg, platelet count range: 3-215k). She had intracranial hemorrhage and anemia at the time of enrollment. During the study she developed severe bleeding events including pulmonary and gastrointestinal hemorrhage, airway bleeding, subarachnoid hemorrhage, and acute respiratory distress. Platelet counts during most bleeding episodes were higher than 50k. Patient died as a result of acute respiratory distress syndrome.

Patient # 92501:
This was a 72 year old white woman with past medical history of pancreatitis, hypertension and arrhythmia, splenectomy and cholecystectomy, cardiac ablation and allergy to heparin, who enrolled in study 209. Baseline platelet was 7k and received a total of 8 doses (2-3mcg/kg) over 1.5 months with platelet count ranging from 7k to 652k.
Patient was hospitalized for portal vein thrombosis, pancreatitis, ascitis, pulmonary consolidation and sepsis. The pancreatitis was assumed to be triggered by portal vein thrombosis. Patient discontinued the study subsequently. The last platelet count was 170k. Three days after study discontinuation, patient developed life threatening adult respiratory distress syndrome with throat Candidiasis requiring intubation and subsequently developed severe gastric hemorrhage. Eventually an intestinal infarction due to superior mesenteric vein thrombosis with a platelet count of 60k occurred. Patient's family decided against bowel resection and only palliative treatment was given. Patient was extubated and died 5 days after the onset of this event.

Patient # 91701:
This patient was a 66 year old white woman who enrolled in study 209 with a medical history consistent of splenectomy, cerebrovascular accident, venous insufficiency, hepatitis C, hypercholesterolemia, hypertension, peptic ulcer, GI bleeding and hepatomegaly. With a baseline platelet count of was 4k, he received 12 weekly Nplate doses ranging between 3-13 mcg/kg and platelet count ranging 2-86k.
Patient developed superficial thrombophlebitis and deep vein thrombosis of right saphenous vein shown by Doppler ultrasound of the legs with bilateral pulmonary embolism for which had an intra vena cava filter placement. However, he died a month later.

Patient # 390301:
This was a 70 year old white man in study 209 and 213, with a medical history of diabetes, liver cirrhosis, hypertension and coronary artery disease, deep vein thrombosis, cerebrovascular accident and cholecystectomy. He received overall 54 weekly doses of Nplate ranging 3-5 mcg/kg with platelet counts between 7k and 201k. During the studies, he developed deep vein thrombosis, acute renal failure, acute MI, and CHF and a right adrenal

mass diagnosed as hepatocellular carcinoma. Nplate was continued. Subsequently he died of cardiopulmonary arrest.

Patient # 301930:
Subject 301930, a 36-year-old Hispanic woman with history of splenectomy, Down syndrome, hypothyroidism, and SLE was randomized to Nplate in study105. Baseline platelet count was 16 x 10^9/L. She received weekly injections of Nplate at doses of 1 or 2 μg/kg over a period of 24 weeks, with corresponding platelet counts fluctuating in the range of 37 to 317 x 10^9/L.

After completion of study 105, she immediately enrolled into Study 213. Nplate doses ranged between1 to 3 μg/kg over a period of 24 weeks with platelet counts between 26 x 10^9/L to 722 x 10^9/L. 1 week after the last dose of Nplate, she was transported to hospital emergency room with respiratory distress, nausea, vomiting, diarrhea, and fever (103.8 °F). She had seizure, hypotension, and then developed ventricular fibrillation and died approximately 7.5 months after the first injection of Nplate in Study 213 and approximately 14 months after initial exposure to Nplate). A blood culture confirmed Streptococcus pneumoniae, and a chest radiograph revealed total opacification of the left lobe. An autopsy report noted the cause of death as acute cardiorespiratory failure secondary to overwhelming postsplenectomy sepsis due to S. pneumoniae.

Patient # 301651:
This patient was a 47-year-old white (Caucasian) woman with relevant history of SLE who was randomized to Nplate in study 212(study 1/ non splenectomized study) with a baseline platelet of 18k. Nplate dose ranged between 1 to 9 μg/kg over 24 weeks and platelet count ranged between16 and 87 x 109/L. Approximately 5 months into study she developed pericardial effusion. In the corresponding study week, platelet count was 5 x 10^9/L(day 148). The event resolved 20 days after onset after administration of proper therapies. The subject continued to receive weekly Nplate over
the duration of the event (9 μg/kg). Patient was immediately enrolled into study 213. She received 2 injections of Nplate at 9 μg/kg (days 1 and 8). She also received prednisone. Patient developed a systemic generalized rash, diarrhea, and vomiting. She was hospitalized with symptoms of fatigue and dyspnea, and developed renal failure (grade moderate), followed by myocardial infarction, congestive heart failure and cardiac arrest, and died approximately 7 months after the initiation of Nplate. The autopsy report listed the final cause of death as acute myocardial infarction and thrombotic microangiopathy of unknown etiology, involving heart, brain, lungs, kidneys, liver, adrenals, and bowel as 1 of the final anatomic diagnoses. Postmortem blood test was positive for antiphospholipid antibodies of IgM type.

Patient # 6051:

This patient was an 80-year-old white man in study 212, randomized to Nplate, with a past medical history of congestive heart failure, hypertension, rectal cancer, partial colectomy, and venous stasis. Baseline platelet count was 9 x 10^9/L. The subject received weekly injections of Nplateover approximately 5 months at doses ranging between 1-3 μg/kg; with corresponding platelet counts ranging between 9 to 167 x 10^9/L. Basal cell carcinoma on face occurred during the study which treated with external beam radiation.

Three days after the last (21st) injection of Nplate at 3 μg/kg, patient was hospitalized for serious, life-threatening, right-sided cerebrovascular accident. Platelet count on the day of the event was 107 x 10^9/L. Treatment included antiplatelet (Aspirin) for 10 days and antihypertensive medications for stroke prevention and furosemide [40 mg, one time only] for congestive heart failure. The subject was discharged to a rehabilitation facility after approximately 2 days of hospitalization. Nplate was permanently discontinued due to this event. Approximately 7 days into rehabilitation, patient developed a serious intracranial hemorrhage. Platelet count on the day of the event was 5 x 10^9/L (platelet count dropped from 107k to 5k after discontinuation of Nplate). Although platelet transfusion was given, his condition deteriorated and he died the next day.

10.4.3 Thromboembolic adverse events:

Patient # 939002: pulmonary embolism (onset date = [redacted]). The subject is a 36-year-old woman with a history of left ventricular hypertrophy, obesity, and on-study hypertension secondary to prednisone who experienced a pulmonary embolism approximately 2.5 weeks after initiation of Nplate. The platelet count was 709 x 10^9/L at the time of the event. The event was considered by the investigator as not related to investigational product. The Applicant's assessment of causality between this event and investigational product was considered to be possibly related. However, the occurrence of the deep vein thrombosis is potentially confounded by the pre-existing history of obesity.

Patient # 951001: deep veinthrombosis (onset date = [redacted] The subject is a 50-year-old woman with a history of type 2 diabetes mellitus, borderline hypertension, and hilar pneumonitis who experienced deep vein thrombosis approximately 2 weeks after initiation of Nplate. The platelet count was 151 x 10^9/L at the time of the event. The event was considered by the investigator as related to investigational product. The occurrence of the deep vein thrombosis is potentially confounded by concurrent use of conjugated estrogen and danazol.

Patient # 740001: pulmonary embolism (onset date = [redacted] . This is a 29-year-old woman with a history of splenectomy, recent fall, and prolonged bed rest who experienced a pulmonary embolism approximately 1 week after the first dose of Nplate. The platelet count was 425 x 10^9/L at that time. The event was considered by the investigator as related to investigational product. The occurrence of pulmonary embolism was potentially confounded by the recent fall and prolonged bed rest.

Results for lupus anticoagulant work-up are pending.

Patient # 131403070: pulmonary embolism (onset date = [redacted]). This is an 82-year-old man with a history of arterial hypertension, type II diabetes mellitus, atrial septal aneurysm, transient ischemic attacks with paresthesia of legs, benign prostatic hypertrophy, adipositas, hyperuricemia, gastritis, thrush oesophagitis, restless leg syndrome, and hyperlipidemia who experienced a pulmonary embolism approximately 5 weeks after initial exposure to Nplate. The platelet count was 31 x 10^9/L at that time. The event was considered by the investigator as related to investigational product.

Patient # : deep vein thrombosis (onset date = [redacted]. This is an 86-year-old man who experienced deep vein thrombosis approximately 11 weeks after initial exposure to Nplate. The event was considered by the investigator as related to investigational product. A query is pending to clarify the nature of this case, including radiographic results.

Patient # 131358071: deep vein thrombosis (onset date = [redacted]). This is a 63-year-old woman with a history of hypertension and obesity who experienced deep vein thrombosis while receiving Nplate approximately 11 days after initiation of investigational product. The event was considered by the investigator as related to investigational product. The occurrence of the deep vein thrombosis is potentially confounded by obesity.

Patient # 113162012: transient ischaemic attack (onset date = [redacted]). This is a 62-year-old man with a history of paroxysmal atrial fibrillation, hyperlipidaemia, and hyperbilirubinemia who experienced a transient ischaemic attack approximately 8 weeks after initiation of Nplate. The event was considered by the investigator as not related to investigational product. The occurrence of the transient ischemic attack is potentially confounded by the history of paroxysmal atrial fibrillation and hyperlipidaemia.

At the time of the marketing application, it was noted that Subject 131207072 in Study 20060131 had a femoral artery occlusion (pain in extremity and edema of lower extremity) based on additional ARISg data (data cutoff = 01 August 2007). Follow-up information for this case received during the 120-day reporting period noted that the term was changed from "femoral artery occlusion" to "pain in extremity" because the occlusion was noted to be a pre-existing condition and had not worsened while on study.

10.4.4 Post-cessation thrombocytopenia

Patient # 1605 : a 43-year-old black man (no splenectomy), reported grade 4 thrombocytopenia on study day 32. Baseline platelet counts were 27 x 10^9/L. On day 15, the platelet count peaked at 543 x 10^9/L and was 276 x 109/L on day 22, making the subject ineligible to receive the second dose of Nplate. Platelets decreased steadily to 2 x 109/L when measured on study day 32 (start date of adverse event). Ongoing prednisone therapy was increased and danazol (200 mg 4 times a day) was initiated. Thrombocytopenia resolved on day 44 when the platelet count was 19 x 10^9/L. The investigator deemed the thrombocytopenia to be possibly related to study drug.

Subject 1624: a 62-year-old white female, developed thrombocytopenia (12 x 10^9/L) with increased bruising and vaginal and rectal bleeding about 3 weeks after completing the full course (6 weeks) of Nplate. During the dosing phase, her peak platelet count peak reached 119 x 10^9/L but decreased to 73 x 10^9/L by the last week of treatment. The subject received emergency room treatment with intravenous gamma globulin, diphenhydramine hydrochloride, acetaminophen, and methylprednisolone. Nine days later, her platelet count was 100 x 10^9/L; the thrombocytopenia and bleeding resolved. The investigator reported the thrombocytopenia as grade 4 (life-threatening), and the bruising and bleeding as moderate. He considered the events medically significant and indicated there was a reasonable possibility that they may have been caused by study drug.

Patient # 6051:
This patient was an 80-year-old white man in study 212, randomized to Nplate, with a past medical history of congestive heart failure, hypertension, rectal cancer, partial colectomy, and venous stasis. Baseline platelet count was 9 x 10^9/L. The subject received weekly injections of Nplate over approximately 5 months at doses ranging between 1-3 μg/kg; with corresponding platelet counts ranging between 9 to 167 x 10^9/L. Basal cell carcinoma on face occurred during the study which treated with external beam radiation. .
Three days after the last (21st) injection of Nplate at 3 μg/kg, patient was hospitalized for serious, life-threatening, right-sided cerebrovascular accident. Platelet count on the day of the event was 107 x 10^9/L. Treatment included antiplatelet (Aspirin) for 10 days and antihypertensive medications for stroke prevention and furosemide [40 mg, one time only] for congestive heart failure. The subject was discharged to a rehabilitation facility after approximately 2 days of hospitalization. Nplate was permanently discontinued due to this event. Approximately 7 days into rehabilitation, patient developed a serious intracranial hemorrhage. Platelet count on the day of the event was 5 x 10^9/L (platelet count dropped from 107k to 5k after discontinuation of Nplate). Although platelet transfusion was given, his condition deteriorated and he died the next day.

Patient # 10302:
A 45 year old ITP patient (enrolled in study 20010218) developed increased lactate dehydrogenase (LDH) as platelet counts rose after the initial SC injection of Nplate: baseline LDH was 379 IU/Land baseline platelet count was 30 x 10^9/L. On study day 9, LDH was 946 IU/L and platelet count 724 x 10^9/L; no elevation in any other serum chemistry value was noted.

Aspirin was given for thrombocytosis . On study day 17, LDH decreased to 545 IU/L , however platelet count increased further to 1062 x 10^9/L; Subject discontinued investigational product. The LDH values and platelet counts resolved toward normal by study day 22 (LDH 378 IU/L, platelet count 447 x 10^9/L).

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