

PRODUCT MONOGRAPH

^{Pr}Nplate™
(romiplostim)

Lyophilized Powder for Solution for Injection
250 mcg/0.5mL and 500 mcg/1mL

Professed Standard

Thrombopoiesis-Stimulating Protein

Amgen Canada Inc.
6775 Financial Drive, Suite 100
Mississauga, Ontario
L5N 0A4

Date of Authorization:
February 19, 2009

Submission Control No: 117327

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION.....	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE.....	4
CONTRAINDICATIONS.....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	7
DRUG INTERACTIONS.....	29
DOSAGE AND ADMINISTRATION.....	29
OVERDOSAGE.....	31
ACTION AND CLINICAL PHARMACOLOGY.....	32
STORAGE AND STABILITY.....	33
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	33
PART II: SCIENTIFIC INFORMATION.....	34
PHARMACEUTICAL INFORMATION.....	34
CLINICAL TRIALS.....	34
DETAILED PHARMACOLOGY.....	47
TOXICOLOGY.....	47
REFERENCES.....	57
PART III: CONSUMER INFORMATION.....	58

PrNplate™
(romiplostim)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medical Ingredients
Subcutaneous	Lyophilized powder for solution for injection / 250 mcg/0.5mL and 500 mcg/1mL	Nplate™ contains small amounts of sugar (mannitol 4% and sucrose 2%). <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

DESCRIPTION

Nplate™ (romiplostim), a member of the TPO mimetic class, is an Fc-peptide fusion protein (peptibody) that activates intracellular transcriptional pathways to increase platelet production via the thrombopoietin (TPO) receptor (also known as cMpl).

The peptibody molecule is comprised of a human immunoglobulin IgG1 Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing two thrombopoietin receptor-binding domains. Nplate™ has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Nplate™ is produced by recombinant DNA technology in *Escherichia coli* (E. coli).

Nplate™ is to be administered by subcutaneous injection. Nplate™ is supplied as a sterile, preservative-free, lyophilized solid white powder for reconstitution. Nplate™ (500 mcg) is reconstituted with 1.2 mL of Sterile Water for Injection, USP and Nplate™ (250 mcg) is reconstituted with 0.72 mL of Sterile Water for Injection, USP. Reconstitution yields a clear, colorless, iso-osmotic solution of Nplate™.

INDICATIONS AND CLINICAL USE

Nplate™ (romiplostim) is indicated to increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP):

- who are nonsplenectomized and have had an inadequate response or are intolerant to corticosteroids and/or immunoglobulins;
- who are splenectomized and have had an inadequate response to splenectomy.

Nplate™ has been used alone or in combination with other ITP therapies such as corticosteroids, azathioprine, or danazol.

CONTRAINDICATIONS

Nplate™ (romiplostim) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container, or with a known history of sensitivity or allergy to any *E. coli*-derived product. For a complete listing of ingredients, see the *Dosage Forms, Composition and Packaging* section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Nplate™ should not be used in patients with myelodysplastic syndromes, outside of a clinical research study, because of the possibility of potentiating the development of myeloid leukemia in such patients.
- Despite ongoing treatment with Nplate™, serious bleeding could occur and patients should be closely monitored during treatment. Rescue medications including platelet transfusions might be required, especially for patients with unstable platelet counts.
- Recurrence of thrombocytopenia, sometimes markedly below pre-treatment baseline levels, and serious life-threatening or fatal bleeding after discontinuation of Nplate™ have been reported.

The following warnings and precautions are observed or theoretical class effects of TPO receptor stimulators.

General

Nplate™ (romiplostim) should be prescribed and monitored only by qualified healthcare providers.

- Nplate™ should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- Nplate™ should not be used in an attempt to normalize platelet counts.

Increased Bone Marrow Reticulin and Risk for Bone Marrow Fibrosis

Nplate™ administration increases the risk for development or progression of reticulin fiber deposition within the bone marrow. Overall, in clinical studies, 10 of 271 (3.7%) were observed to have reticulin in the bone marrow. Nplate™ was discontinued in 4 of the 271 (1.5%) patients because of bone marrow reticulin deposition. Six (2.2%) additional patients had reticulin observed upon bone marrow biopsy. All 10 patients with bone marrow reticulin deposition had 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. In the extension study, one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate™ therapy. Clinical studies have not excluded a risk of bone marrow fibrosis with cytopenias with Nplate™.

Following identification of a stable Nplate™ dose, examine peripheral blood smears and complete blood counts (CBCs) monthly for new or worsening morphological abnormalities (eg, teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Nplate™ and consider a bone marrow biopsy, including staining for fibrosis.

The long term risk for progression to myelofibrosis is unknown.

Recurrence of Thrombocytopenia and Bleeding After Cessation of Treatment

Thrombocytopenia is likely to recur upon discontinuation of Nplate™. There is an increased risk for bleeding if Nplate™ is discontinued in the presence of anticoagulants or anti-platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of Nplate™. It is recommended that, if treatment with Nplate™ is discontinued, weekly platelet counts should be obtained for at least two weeks and ITP treatment should be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support.

In clinical studies of patients with chronic ITP who had Nplate™ discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present prior to Nplate™ therapy. This worsened thrombocytopenia resolved within 14 days; rescue treatments were required to resolve it.

Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of Nplate™ or medication errors that result in excessive Nplate™ doses may produce thrombocytosis and thrombotic/thromboembolic complications. In controlled clinical studies, the incidence of thrombotic/thromboembolic complications was 2.4% in both Nplate™ and placebo. To minimize the risk for thrombocytosis, do not use Nplate™ in an attempt to "normalize" platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of $\geq 50 \times 10^9/L$ see *Dosage and Administration*.

Of the 271 patients who received Nplate™ in ITP clinical studies, the study duration adjusted thrombotic/thromboembolic rate in subjects with age 65 and over was 22.9 per 100-subject year compared with 4.1 per 100-subject year in the < 65 years age group (see *Warnings and Precautions, Special Populations – Geriatrics*).

As a note the venous thrombotic/thromboembolic event ratios between age 65 and over vs. younger are in line with general population (*Silverstein M.D.et al, 1998*).

Lack or Loss of Response to Nplate™

Hyporesponsiveness or failure to maintain a platelet response with Nplate™ within the recommended dosing range should prompt a search for causative factors including immunogenicity and increased bone marrow reticulin (see *Adverse Reactions - Immunogenicity and Warnings and Precautions – Increased Bone Marrow Reticulin*). Discontinue Nplate™ if the platelet count does not increase to $\geq 50 \times 10^9/L$ or to a level sufficient to avoid clinically important bleeding after four weeks at the highest weekly dose of 10 mcg/kg (see *Dosage and Administration, Treatment Discontinuation*).

Malignancies and Progression of Malignancies

Stimulation of the thrombopoietin (TPO) receptor on the surface of hematopoietic cells may increase the risk for hematologic malignancies. In controlled clinical studies among patients with chronic ITP, the incidence of hematologic malignancy was 1.2 % in Nplate™ - treated patients versus 2.4 % in patients treated with placebo. In a separate single-arm clinical study of 44 patients with myelodysplastic syndromes (MDS), 11 patients were reported as having possible disease progression, among whom 4 patients had confirmation of acute myelogenous leukemia (AML) during follow-up. Nplate™ is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

Laboratory Monitoring

Monitor CBCs, including platelet counts, prior to initiation, throughout and following discontinuation of Nplate™ therapy. Prior to the initiation of Nplate™, examine the peripheral blood differential to establish the baseline extent of red and white blood cell abnormalities. Obtain CBCs, including platelet counts, weekly during the dose adjustment phase of Nplate™ therapy and then monthly following establishment of a stable Nplate™ dose. Obtain CBCs, including platelet counts weekly for at least two weeks following discontinuation of Nplate™.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies of Nplate™ in pregnant women. Nplate™ should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus or embryo.

Nursing Women:

It is not known whether Nplate™ is excreted in human milk. Caution should be exercised when Nplate™ is administered to women who are breast-feeding. 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.

Pediatrics:

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

Geriatrics:

Of the 271 patients who received Nplate™ in ITP clinical studies, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. Due to the limited number of older patients, no definitive conclusions can be made with regards to the impact of age on efficacy or safety. The study duration adjusted thrombotic/thromboembolic rate in subjects with age 65 and over was 22.9 per 100-subject year compared with 4.1 per 100-subject year in the < 65 years age group. As a note the venous thrombotic/thromboembolic event ratios between age 65 and over vs. younger are in line with general population (*Silverstein M.D.et al, 1998*).

Hepatic Impairment:

Experience is limited in patients with severe hepatic impairment. Nplate™ should be used with caution in this population.

Renal impairment:

Experience is limited in patients with severe renal impairment. Nplate™ should be used with caution in this population.

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

Thrombocytopenia is likely to recur upon discontinuation of Nplate™ (romiplostim). Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding. Increased bone marrow reticulin has been observed in some ITP patients treated with Nplate™. This finding may be suggested by morphological changes in the peripheral blood cells and can be detected by bone marrow biopsy. Platelet counts above the normal range present a theoretical risk for thrombotic / thromboembolic complications; dose adjustment guidelines should be followed. Please see *Warnings and Precautions: Thrombotic/Thromboembolic Complications*.

In the Phase 3, placebo-controlled trials, the most common adverse drug reactions were headache, arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, paresthesia.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Serious adverse reactions associated with Nplate™ in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate™ discontinuation.

The data described below reflect Nplate™ exposure to 271 patients with chronic ITP, age 18 to 88, of whom 62% were female. Nplate™ was studied in two randomized, placebo-controlled, double-blind studies that were identical in design, with the exception that Study 1 (Table 1 and Table 3) evaluated nonsplenectomized patients with ITP and Study 2 (Table 2 and Table 4) evaluated splenectomized patients with ITP. Data are also reported from an open label, single arm study in which patients received Nplate™ over an extended period of time. Overall,

Nplate™ was administered to 114 patients for at least 52 weeks and 53 patients for at least 96 weeks.

In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction. In nonsplenectomized patients, headaches occurred in 26% of patients receiving Nplate™ and 30% of patients receiving placebo. In splenectomized patients, headaches occurred in 43% of patients receiving Nplate™ and 33% of patients receiving placebo. Headaches were usually of mild or moderate severity.

Adverse Reactions from Nplate™ Phase 3 Placebo Controlled ITP Studies

Table 1 and Table 2 presents adverse drug reactions from the two Phase 3 placebo-controlled studies (Study 1 and Study 2; n=125) at a frequency ≥1%. The majority of these adverse drug reactions were mild to moderate in severity. Table 3 and Table 4 presents adverse events with a ≥ 2% difference (Nplate™ verses placebo) in nonsplenectomized (Study 1) and splenectomized (Study 2) patients.

Table 1: Adverse Drug Reactions ≥1% Identified in Study 1 (Nonsplenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 20)
Preferred Term	n (%)	n (%)
Headache	11 (26.2)	6 (30.0)
Arthralgia	10 (23.8)	5 (25.0)
Pain in extremity	8 (19.0)	2 (10.0)
Dizziness	7 (16.7)	0 (0)
Insomnia	5 (11.9)	2 (10.0)
Abdominal pain	5 (11.9)	0 (0)
Shoulder pain	5 (11.9)	0 (0)
Myalgia	3 (7.1)	1 (5.0)
Dyspepsia	2 (4.8)	0 (0)
Paresthesia	2 (4.8)	0 (0)

* Note: one patient randomized to placebo in Study S1 (212) actually received Nplate™ and is included in the Nplate™ group.

**Table 2: Adverse Drug Reactions \geq 1% Identified in Study 2
(Splenectomized Patients)**

	Nplate™ (N = 42)	Placebo (N = 21)
Preferred Term	n (%)	n (%)
Headache	18 (42.9)	7 (33.3)
Arthralgia	12 (28.6)	3 (14.3)
Myalgia	9 (21.4)	0 (0)
Insomnia	8 (19.0)	1 (4.8)
Dizziness	7 (16.7)	0 (0)
Abdominal pain	4 (9.5)	0 (0)
Dyspepsia	4 (9.5)	0 (0)
Pain in extremity	3 (7.1)	0 (0)
Paresthesia	3 (7.1)	0 (0)
Shoulder pain	2 (4.8)	0 (0)
Bone marrow disorder ^a	1 (2.4)	0 (0)

^a Actual frequency is unknown since routine bone marrow biopsies were not performed, see *Warnings and Precautions - Increased Bone Marrow Reticulin*

Table 3: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 1 (Nonsplenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 20)
Preferred Term	n (%)	n (%)
Epistaxis	11 (26.2)	3 (15.0)
Pain in Extremity	8 (19.0)	2 (10.0)
Dizziness	7 (16.7)	0 (0)
Nausea	6 (14.3)	2 (10.0)
Upper Respiratory Tract Infection	6 (14.3)	2 (10.0)
Back Pain	6 (14.3)	1 (5.0)
Gingival Bleeding	5 (11.9)	1 (5.0)
Injection Site Bruising	5 (11.9)	1 (5.0)
Abdominal Pain	5 (11.9)	0 (0)
Shoulder Pain	5 (11.9)	0 (0)
Myalgia	3 (7.1)	1 (5.0)
Anemia	3 (7.1)	0 (0)
Excoriation	3 (7.1)	0 (0)
Pruritus	3 (7.1)	0 (0)
Depression	2 (4.8)	0 (0)
Dysarthria	2 (4.8)	0 (0)
Dyspepsia	2 (4.8)	0 (0)
Flatulence	2 (4.8)	0 (0)
Herpes Simplex	2 (4.8)	0 (0)
Hydronephrosis	2 (4.8)	0 (0)
Paresthesia	2 (4.8)	0 (0)
Splenomegaly	2 (4.8)	0 (0)
Allergic Sinusitis	1 (2.4)	0 (0)
Anal Fissure	1 (2.4)	0 (0)
Arthritis	1 (2.4)	0 (0)
B-Cell Lymphoma	1 (2.4)	0 (0)
Basal Cell Carcinoma	1 (2.4)	0 (0)
Bladder Pain	1 (2.4)	0 (0)
Blood Pressure Increased	1 (2.4)	0 (0)
Bone Pain	1 (2.4)	0 (0)
Burning Sensation	1 (2.4)	0 (0)
Carotid Bruit	1 (2.4)	0 (0)
Cerebrovascular Accident	1 (2.4)	0 (0)
Chest Pain	1 (2.4)	0 (0)
Coccydynia	1 (2.4)	0 (0)
Confusional State	1 (2.4)	0 (0)

Table 3: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 1 (Nonsplenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 20)
Preferred Term	n (%)	n (%)
Conjunctivitis Infective	1 (2.4)	0 (0)
Constipation	1 (2.4)	0 (0)
Dental Caries	1 (2.4)	0 (0)
Diabetes Mellitus	1 (2.4)	0 (0)
Dysphonia	1 (2.4)	0 (0)
Dyspnea Exertional	1 (2.4)	0 (0)
Ear Congestion	1 (2.4)	0 (0)
Ear Infection	1 (2.4)	0 (0)
Erythema	1 (2.4)	0 (0)
Eye Pruritus	1 (2.4)	0 (0)
Gastritis	1 (2.4)	0 (0)
Gastroenteritis Viral	1 (2.4)	0 (0)
Gastrointestinal Hemorrhage	1 (2.4)	0 (0)
Genital Infection Fungal	1 (2.4)	0 (0)
Hematochezia	1 (2.4)	0 (0)
Hemoptysis	1 (2.4)	0 (0)
Hemorrhage Intracranial	1 (2.4)	0 (0)
Head Injury	1 (2.4)	0 (0)
Hepatic Steatosis	1 (2.4)	0 (0)
Hiatus Hernia	1 (2.4)	0 (0)
Hot Flush	1 (2.4)	0 (0)
Hypersensitivity	1 (2.4)	0 (0)
Hypertension	1 (2.4)	0 (0)
Hypertensive Crisis	1 (2.4)	0 (0)
Hypothyroidism	1 (2.4)	0 (0)
Hypotrichosis	1 (2.4)	0 (0)
Increased Appetite	1 (2.4)	0 (0)
Influenza Like Illness	1 (2.4)	0 (0)
Injection Site Discomfort	1 (2.4)	0 (0)
Injection Site Pain	1 (2.4)	0 (0)
Joint Stiffness	1 (2.4)	0 (0)
Keratoconjunctivitis Sicca	1 (2.4)	0 (0)
Lethargy	1 (2.4)	0 (0)
Lip Hemorrhage	1 (2.4)	0 (0)
Muscle Strain	1 (2.4)	0 (0)
Muscular Weakness	1 (2.4)	0 (0)
Musculoskeletal Chest Pain	1 (2.4)	0 (0)
Musculoskeletal Pain	1 (2.4)	0 (0)

Table 3: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 1 (Nonsplenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 20)
Preferred Term	n (%)	n (%)
Musculoskeletal Stiffness	1 (2.4)	0 (0)
Non-Cardiac Chest Pain	1 (2.4)	0 (0)
Edema Peripheral	1 (2.4)	0 (0)
Oral Infection	1 (2.4)	0 (0)
Pericardial Effusion	1 (2.4)	0 (0)
Pleural Effusion	1 (2.4)	0 (0)
Pollakiuria	1 (2.4)	0 (0)
Renal Artery Stenosis	1 (2.4)	0 (0)
Road Traffic Accident	1 (2.4)	0 (0)
Sciatica	1 (2.4)	0 (0)
Scratch	1 (2.4)	0 (0)
Sinus Headache	1 (2.4)	0 (0)
Skin Discolouration	1 (2.4)	0 (0)
Skin Warm	1 (2.4)	0 (0)
Sternal Fracture	1 (2.4)	0 (0)
Suicidal Ideation	1 (2.4)	0 (0)
Tendonitis	1 (2.4)	0 (0)
Thermal Burn	1 (2.4)	0 (0)
Tremor	1 (2.4)	0 (0)
Umbilical Hernia	1 (2.4)	0 (0)
Urinary Hesitation	1 (2.4)	0 (0)
Urine Abnormality	1 (2.4)	0 (0)
Viral Infection	1 (2.4)	0 (0)
Vision Blurred	1 (2.4)	0 (0)
Weight Increased	1 (2.4)	0 (0)
Wound	1 (2.4)	0 (0)

Table 4: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 2 (Splenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 21)
Preferred Term	n (%)	n (%)
Headache	18 (42.9)	7 (33.3)
Epistaxis	16 (38.1)	7 (33.3)
Fatigue	13 (31.0)	5 (23.8)
Arthralgia	12 (28.6)	3 (14.3)
Diarrhea	9 (21.4)	2 (9.5)
Myalgia	9 (21.4)	0 (0)
Contusion	8 (19.0)	3 (14.3)
Upper Respiratory Tract Infection	8 (19.0)	3 (14.3)
Insomnia	8 (19.0)	1 (4.8)
Cough	7 (16.7)	3 (14.3)
Dizziness	7 (16.7)	0 (0)
Pain	6 (14.3)	2 (9.5)
Pharyngolaryngeal Pain	6 (14.3)	0 (0)
Pyrexia	6 (14.3)	0 (0)
Muscle Spasms	5 (11.9)	2 (9.5)
Nausea	5 (11.9)	2 (9.5)
Edema Peripheral	5 (11.9)	2 (9.5)
Oral Mucosal Blistering	5 (11.9)	2 (9.5)
Asthenia	5 (11.9)	1 (4.8)
Injection Site Pain	4 (9.5)	1 (4.8)
Vomiting	4 (9.5)	1 (4.8)
Abdominal Pain	4 (9.5)	0 (0)
Dyspepsia	4 (9.5)	0 (0)
Hematoma	4 (9.5)	0 (0)
Alopecia	3 (7.1)	1 (4.8)
Influenza	3 (7.1)	1 (4.8)
Injection Site Bruising	3 (7.1)	1 (4.8)
Chills	3 (7.1)	0 (0)
Musculoskeletal Chest Pain	3 (7.1)	0 (0)
Pain in Extremity	3 (7.1)	0 (0)
Paresthesia	3 (7.1)	0 (0)
Rhinitis Allergic	3 (7.1)	0 (0)
Viral Upper Respiratory Tract Infection	3 (7.1)	0 (0)
Weight Increased	3 (7.1)	0 (0)
Abdominal Pain Upper	2 (4.8)	0 (0)
Acne	2 (4.8)	0 (0)
Angina Pectoris	2 (4.8)	0 (0)

Table 4: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 2 (Splenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 21)
Preferred Term	n (%)	n (%)
Blood Pressure Increased	2 (4.8)	0 (0)
Bone Pain	2 (4.8)	0 (0)
Bronchitis	2 (4.8)	0 (0)
Candidiasis	2 (4.8)	0 (0)
Flushing	2 (4.8)	0 (0)
Hematochezia	2 (4.8)	0 (0)
Hemoptysis	2 (4.8)	0 (0)
Hot Flush	2 (4.8)	0 (0)
Lacrimation Increased	2 (4.8)	0 (0)
Menorrhagia	2 (4.8)	0 (0)
Metrorrhagia	2 (4.8)	0 (0)
Migraine	2 (4.8)	0 (0)
Muscular Weakness	2 (4.8)	0 (0)
Nasal Congestion	2 (4.8)	0 (0)
Edema	2 (4.8)	0 (0)
Shoulder Pain	2 (4.8)	0 (0)
Skin Hemorrhage	2 (4.8)	0 (0)
Sleep Apnea Syndrome	2 (4.8)	0 (0)
Thrombocytopenia	2 (4.8)	0 (0)
Acarodermatitis	1 (2.4)	0 (0)
Alanine Aminotransferase Increased	1 (2.4)	0 (0)
Allergic Sinusitis	1 (2.4)	0 (0)
Angioneurotic Edema	1 (2.4)	0 (0)
Aphthous Stomatitis	1 (2.4)	0 (0)
Appendicitis	1 (2.4)	0 (0)
Aspartate Aminotransferase Increased	1 (2.4)	0 (0)
Body Tinea	1 (2.4)	0 (0)
Bone Marrow Disorder	1 (2.4)	0 (0)
Breath Odour	1 (2.4)	0 (0)
Cardiac Failure Congestive	1 (2.4)	0 (0)
Cellulitis	1 (2.4)	0 (0)
Cholelithiasis	1 (2.4)	0 (0)
Constipation	1 (2.4)	0 (0)
Dehydration	1 (2.4)	0 (0)
Dermal Cyst	1 (2.4)	0 (0)
Disturbance in Attention	1 (2.4)	0 (0)
Dry Skin	1 (2.4)	0 (0)
Dry Throat	1 (2.4)	0 (0)

Table 4: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 2 (Splenuctomized Patients)

	Nplate™ (N = 42)	Placebo (N = 21)
Preferred Term	n (%)	n (%)
Dysgeusia	1 (2.4)	0 (0)
Dysmenorrhea	1 (2.4)	0 (0)
Dysphonia	1 (2.4)	0 (0)
Ear Hemorrhage	1 (2.4)	0 (0)
Excoriation	1 (2.4)	0 (0)
Extrasystoles	1 (2.4)	0 (0)
Face Edema	1 (2.4)	0 (0)
Fall	1 (2.4)	0 (0)
Fungal Infection	1 (2.4)	0 (0)
Gastroenteritis	1 (2.4)	0 (0)
Gastrointestinal Infection	1 (2.4)	0 (0)
Goitre	1 (2.4)	0 (0)
Gynecomastia	1 (2.4)	0 (0)
Hair Growth Abnormal	1 (2.4)	0 (0)
Heart Rate Increased	1 (2.4)	0 (0)
Hepatitis C Antibody Positive	1 (2.4)	0 (0)
Herpes Simplex	1 (2.4)	0 (0)
Hypersensitivity	1 (2.4)	0 (0)
Hypoesthesia	1 (2.4)	0 (0)
Hypokalemia	1 (2.4)	0 (0)
Hypovolemia	1 (2.4)	0 (0)
Idiopathic Thrombocytopenic Purpura	1 (2.4)	0 (0)
Influenza Like Illness	1 (2.4)	0 (0)
Injection Site Swelling	1 (2.4)	0 (0)
Intervertebral Disc Protrusion	1 (2.4)	0 (0)
Lip Blister	1 (2.4)	0 (0)
Mouth Hemorrhage	1 (2.4)	0 (0)
Musculoskeletal Stiffness	1 (2.4)	0 (0)
Nail Disorder	1 (2.4)	0 (0)
Nightmare	1 (2.4)	0 (0)
Ocular Hyperaemia	1 (2.4)	0 (0)
Oral Candidiasis	1 (2.4)	0 (0)
Paranasal Sinus Hypersecretion	1 (2.4)	0 (0)
Peripheral Embolism	1 (2.4)	0 (0)
Peripheral Ischemia	1 (2.4)	0 (0)
Petit Mal Epilepsy	1 (2.4)	0 (0)
Pharyngitis	1 (2.4)	0 (0)
Photosensitivity Reaction	1 (2.4)	0 (0)

Table 4: Adverse Events with $\geq 2\%$ difference (Nplate™ vs. Placebo) in Study 2 (Splenectomized Patients)

	Nplate™ (N = 42)	Placebo (N = 21)
Preferred Term	n (%)	n (%)
Pleural Effusion	1 (2.4)	0 (0)
Postmenopausal Hemorrhage	1 (2.4)	0 (0)
Prurigo	1 (2.4)	0 (0)
Psychomotor Hyperactivity	1 (2.4)	0 (0)
Rash Papular	1 (2.4)	0 (0)
Rectal Hemorrhage	1 (2.4)	0 (0)
Scleral Hemorrhage	1 (2.4)	0 (0)
Seasonal Allergy	1 (2.4)	0 (0)
Skin Infection	1 (2.4)	0 (0)
Skin Lesion	1 (2.4)	0 (0)
Skin Odour Abnormal	1 (2.4)	0 (0)
Soft Tissue Injury	1 (2.4)	0 (0)
Sputum Discoloured	1 (2.4)	0 (0)
Stomach Discomfort	1 (2.4)	0 (0)
Suicide Attempt	1 (2.4)	0 (0)
Syncope	1 (2.4)	0 (0)
Tendonitis	1 (2.4)	0 (0)
Tension Headache	1 (2.4)	0 (0)
Tinnitus	1 (2.4)	0 (0)
Tongue Injury	1 (2.4)	0 (0)
Tooth Discolouration	1 (2.4)	0 (0)
Tooth Infection	1 (2.4)	0 (0)
Uterine Polyp	1 (2.4)	0 (0)
Vaginal Hemorrhage	1 (2.4)	0 (0)
Viral Infection	1 (2.4)	0 (0)
Visual Disturbance	1 (2.4)	0 (0)
Visual Field Defect	1 (2.4)	0 (0)
Vitamin B12 Deficiency	1 (2.4)	0 (0)
Vulvovaginal Mycotic Infection	1 (2.4)	0 (0)
Weight Decreased	1 (2.4)	0 (0)
Wound	1 (2.4)	0 (0)

Long-term ITP Extension Study

An interim analysis was done for subjects from 6 ITP studies who completed their parent study and entered the ongoing open label extension study 20030213. A total of 137 subjects were enrolled, and 136 subjects received at least 1 dose of Nplate™. At the time of the interim analysis, the mean time on study for the 136 subjects in the safety analysis set was 45 weeks (SD, 34.7 weeks; range, 1 to 122 weeks).

Adverse events with a subject incidence $\geq 10\%$ were headache (30.9%), contusion (26.5%), fatigue (24.3%), diarrhea (23.5%), epistaxis (22.8%), nasopharyngitis (21.3%), arthralgia (19.9%), upper respiratory tract infection (17.6%), cough (16.2%), nausea (15.4%), back pain (14.7%), petechiae (14.0%), dizziness (12.5%), pain in extremity (12.5%), peripheral edema (11.8%), oral mucosal blistering (11.8%), gingival bleeding (11.0%), hematoma (11.0%), and rash (11.0%).

Adverse events were reported as treatment-related for 47 subjects (34.6%). Serious adverse events were reported for 35 subjects (25.7%). Adverse events leading to study withdrawal were reported for 8 (5.9%) subjects.

Nine serious thrombotic or thromboembolic events were reported in 6 subjects ($6/136 = 4.4\%$). Reports that mentioned fibrosis or reticulin in the bone marrow were received for 7 subjects. In addition, bone marrow reticulin was noted in reports of adverse events in 2 other subjects. Three subjects died during this study. None of the deaths were considered treatment related.

Table 5, Table 6, Table 7 and Table 8 presents; Adverse Drug Reactions with a subject incidence $\geq 1\%$; Adverse Events with a subject incidence $\geq 2\%$; Serious Adverse Events; and Adverse Events leading to study withdrawal, respectively, for the long term ITP extension study.

Table 5: Subject Incidence of Adverse Drug Reactions with Subject Incidence $\geq 1\%$

	Nplate™ (N = 136)
Preferred Term	n (%)
Headache	42 (30.9)
Arthralgia	27 (19.9)
Dizziness	17 (12.5)
Pain In Extremity	17 (12.5)
Abdominal Pain	13 (9.6)
Insomnia	13 (9.6)
Myalgia	9 (6.6)
Paresthesia	9 (6.6)
Dyspepsia	6 (4.4)
Bone Marrow Disorder	4 (2.9)
Shoulder Pain	3 (2.2)

Table 6: Subject Incidence of Adverse Events With Subject Incidence $\geq 2\%$	
	Nplate™ (N = 136)
Preferred Term	n (%)
Headache	42 (30.9)
Contusion	36 (26.5)
Fatigue	33 (24.3)
Diarrhea	32 (23.5)
Epistaxis	31 (22.8)
Nasopharyngitis	29 (21.3)
Arthralgia	27 (19.9)
Upper Respiratory Tract Infection	24 (17.6)
Cough	22 (16.2)
Nausea	21 (15.4)
Back Pain	20 (14.7)
Petechiae	19 (14.0)
Dizziness	17 (12.5)
Pain In Extremity	17 (12.5)
Edema Peripheral	16 (11.8)
Oral Mucosal Blistering	16 (11.8)
Gingival Bleeding	15 (11.0)
Hematoma	15 (11.0)
Rash	15 (11.0)
Abdominal Pain	13 (9.6)
Insomnia	13 (9.6)
Muscle Spasms	13 (9.6)
Pain	13 (9.6)
Pharyngolaryngeal Pain	13 (9.6)
Sinusitis	13 (9.6)
Rhinorrhea	12 (8.8)
Injection Site Bruising	11 (8.1)

Table 6: Subject Incidence of Adverse Events With Subject Incidence $\geq 2\%$	
	Nplate™ (N = 136)
Preferred Term	n (%)
Pyrexia	11 (8.1)
Vomiting	11 (8.1)
Depression	9 (6.6)
Myalgia	9 (6.6)
Paresthesia	9 (6.6)
Thrombocytopenia	9 (6.6)
Constipation	8 (5.9)
Ecchymosis	8 (5.9)
Sinus Headache	8 (5.9)
Urinary Tract Infection	8 (5.9)
Asthenia	7 (5.1)
Dyspnea	7 (5.1)
Procedural Pain	7 (5.1)
Pruritus	7 (5.1)
Abdominal Discomfort	6 (4.4)
Dyspepsia	6 (4.4)
Injection Site Pain	6 (4.4)
Joint Swelling	6 (4.4)
Abdominal Pain Upper	5 (3.7)
Anxiety	5 (3.7)
Chills	5 (3.7)
Dysuria	5 (3.7)
Ear Infection	5 (3.7)
Eczema	5 (3.7)
Herpes Simplex	5 (3.7)
Joint Sprain	5 (3.7)
Migraine	5 (3.7)
Mouth Hemorrhage	5 (3.7)
Nasal Congestion	5 (3.7)

Table 6: Subject Incidence of Adverse Events With Subject Incidence $\geq 2\%$

	Nplate™ (N = 136)
Preferred Term	n (%)
Pharyngitis	5 (3.7)
Purpura	5 (3.7)
Skin Lesion	5 (3.7)
Toothache	5 (3.7)
Vaginal Hemorrhage	5 (3.7)
Bone Marrow Disorder	4 (2.9)
Cardiac Failure Congestive	4 (2.9)
Conjunctival Hemorrhage	4 (2.9)
Dehydration	4 (2.9)
Excoriation	4 (2.9)
Fall	4 (2.9)
Gastroenteritis	4 (2.9)
Hemorrhage	4 (2.9)
Hypersensitivity	4 (2.9)
Hypertension	4 (2.9)
Hypoesthesia	4 (2.9)
Influenza	4 (2.9)
Menorrhagia	4 (2.9)
Musculoskeletal Chest Pain	4 (2.9)
Sciatica	4 (2.9)
Seasonal Allergy	4 (2.9)
Stomatitis	4 (2.9)
Swelling Face	4 (2.9)
Viral Upper Respiratory Tract Infection	4 (2.9)
Anemia	3 (2.2)
Arthropod Bite	3 (2.2)
Asthma	3 (2.2)
Chest Discomfort	3 (2.2)
Cystitis	3 (2.2)

Table 6: Subject Incidence of Adverse Events With Subject Incidence $\geq 2\%$	
	Nplate™ (N = 136)
Preferred Term	n (%)
Dyspnea Exertional	3 (2.2)
Ear Hemorrhage	3 (2.2)
Ear Pain	3 (2.2)
Erythema	3 (2.2)
Eye Pain	3 (2.2)
Hemoptysis	3 (2.2)
Influenza Like Illness	3 (2.2)
Limb Injury	3 (2.2)
Malaise	3 (2.2)
Metrorrhagia	3 (2.2)
Musculoskeletal Stiffness	3 (2.2)
Neck Pain	3 (2.2)
Oral Mucosal Petechiae	3 (2.2)
Osteoarthritis	3 (2.2)
Pneumonia	3 (2.2)
Renal Failure	3 (2.2)
Rhinitis	3 (2.2)
Shoulder Pain	3 (2.2)
Urticaria	3 (2.2)
Vision Blurred	3 (2.2)

Table 7: Subject Incidence of Serious Adverse Events	
	Nplate™ (N = 136)
Preferred Term	n (%)
Thrombocytopenia	8 (5.9)
Bone Marrow Disorder	3 (2.2)
Abdominal Pain	2 (1.5)
Cardiac Failure Congestive	2 (1.5)
Gingival Bleeding	2 (1.5)
Platelet Count Increased	2 (1.5)
Pneumonia	2 (1.5)
Pyrexia	2 (1.5)
Renal Failure	2 (1.5)
Thrombosis	2 (1.5)
Acute Myocardial Infarction	1 (0.7)
Adverse Drug Reaction	1 (0.7)
Anemia	1 (0.7)
Anal Fistula	1 (0.7)
Anxiety	1 (0.7)
Asthma	1 (0.7)
Atrial Fibrillation	1 (0.7)
Blindness	1 (0.7)
Cardiac Arrest	1 (0.7)
Catheter Related Infection	1 (0.7)
Cerebral Thrombosis	1 (0.7)
Cholecystitis	1 (0.7)
Deep Vein Thrombosis	1 (0.7)
Dehydration	1 (0.7)
Device Related Infection	1 (0.7)
Dyspnea	1 (0.7)

Table 7: Subject Incidence of Serious Adverse Events

Preferred Term	Nplate™ (N = 136) n (%)
Epistaxis	1 (0.7)
Evan's Syndrome	1 (0.7)
Gastric Ulcer Hemorrhage	1 (0.7)
Gastritis	1 (0.7)
Gastrointestinal Hemorrhage	1 (0.7)
Hematoma	1 (0.7)
Hemoptysis	1 (0.7)
Headache	1 (0.7)
Hepatic Failure	1 (0.7)
Hepatic Neoplasm Malignant	1 (0.7)
Hepatitis	1 (0.7)
Hypertension	1 (0.7)
Idiopathic Thrombocytopenic Purpura	1 (0.7)
Knee Arthroplasty	1 (0.7)
Mechanical Complication Of Implant	1 (0.7)
Melaena	1 (0.7)
Metrorrhagia	1 (0.7)
Multiple Myeloma	1 (0.7)
Multiple Sclerosis Relapse	1 (0.7)
Myelofibrosis	1 (0.7)
Oral Mucosal Petechiae	1 (0.7)
Osteoarthritis	1 (0.7)
Papilloedema	1 (0.7)
Petechiae	1 (0.7)
Plastic Surgery	1 (0.7)
Platelet Count Decreased	1 (0.7)
Pneumonia Pneumococcal	1 (0.7)
Portal Vein Thrombosis	1 (0.7)
Post Procedural Cellulitis	1 (0.7)

Table 7: Subject Incidence of Serious Adverse Events	
	Nplate™ (N = 136)
Preferred Term	n (%)
Renal Failure Acute	1 (0.7)
Salpingo-Oophorectomy	1 (0.7)
Surgery	1 (0.7)
Thrombophlebitis Septic	1 (0.7)
Transient Ischemic Attack	1 (0.7)
Upper Gastrointestinal Hemorrhage	1 (0.7)
Urosepsis	1 (0.7)
Vaginal Hemorrhage	1 (0.7)

Table 8: Subject Incidence of Adverse Events Leading to Study Withdrawal	
	Nplate™ (N = 136)
Preferred Term	n (%)
Cardiac Arrest	1 (0.7)
Headache	1 (0.7)
Hepatic Failure	1 (0.7)
Multiple Myeloma	1 (0.7)
Musculoskeletal Pain	1 (0.7)
Myelofibrosis	1 (0.7)
Pneumonia Pneumococcal	1 (0.7)
Renal Failure	1 (0.7)
Thrombophlebitis Septic	1 (0.7)
Vaginal Hemorrhage	1 (0.7)

Bleeding Events

Across the entire ITP clinical programme, an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (\geq grade 3) bleeding events occurred at platelet counts $< 30 \times 10^9/L$. All bleeding events \geq grade 2 occurred at platelet counts $< 50 \times 10^9/L$.

In the Phase 3 studies, 9 patients reported a bleeding event that was considered serious (5 [6.0%] Nplate, 4 [9.8%] placebo). When adjusted for study duration, serious bleeding events were reported at 16.6 and 26.9 per 100 patient-years for Nplate™ and placebo, respectively.

Bleeding events that were grade 2 or higher were reported by 15% of patients treated with Nplate and 34% of patients treated with placebo. When adjusted for study duration, bleeding events grade 2 or higher were reported at 118.4 per and 134.4 per 100 patient-years for Nplate™ and placebo, respectively.

In the Phase 3 ITP long-term safety set, the study duration adjusted event rate of grade 2 or higher bleeding events was 71 per 100 patient-years for patients treated with Nplate™ and 132 per 100 patient-years for placebo treated patients.

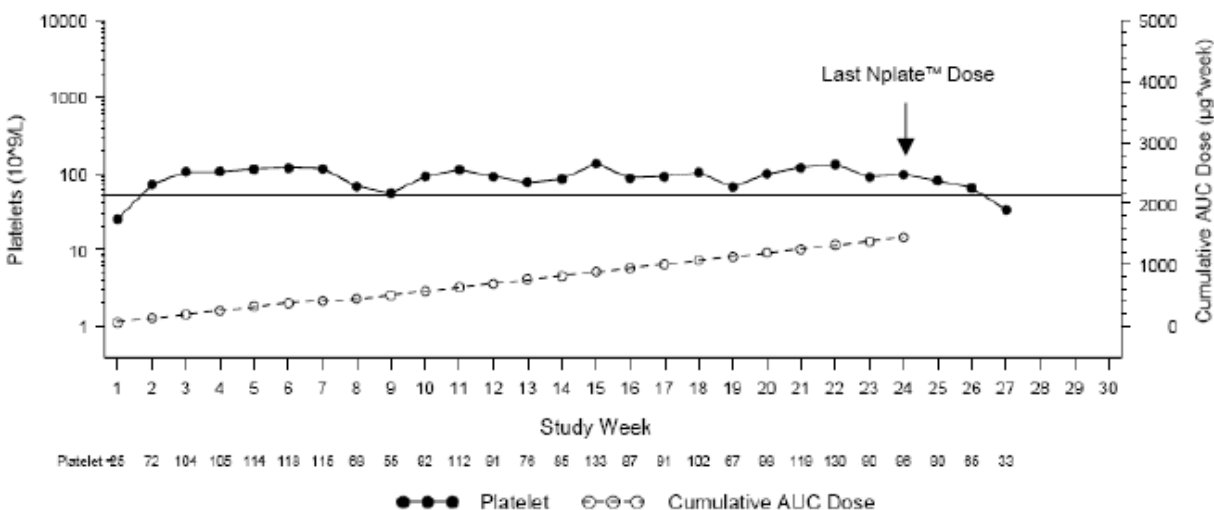
Bleeding events in Subjects with Variable Platelet Counts (Unstable Platelet Counts)

Nine (7%) subjects in the pivotal studies had platelet counts that rose and fell to extreme levels within short periods of time; these subjects' course on study often included multiple rescue medications and numerous Nplate™ dose adjustments. Among these subjects 6 were treated with Nplate™ and 3 were treated with placebo. In addition 7 of the 9 subjects had been splenectomized. Nplate™ treated subjects had wider platelet count ranges with higher upper limits compared to those with placebo, possibly due to the effect of Nplate™ alone or synergistic effect with rescue medications.

As a result of the many severe declines in platelet count, these subjects experienced numerous bleeding events, including severe and serious bleeding events, and a life threatening hemorrhage. These 9 subjects highlight the individual variability that is found in ITP and the challenges of managing patients whose platelet counts cannot be stabilized, in contrast to subjects who were able to achieve a stable response.

Figure 1 and Figure 2 provide a representation of two individual subjects treated with Nplate™ who experienced stable and unstable platelet counts, respectively.

Figure 1: Individual Platelet Count and Cumulative Dose Over Time: Durable Responder

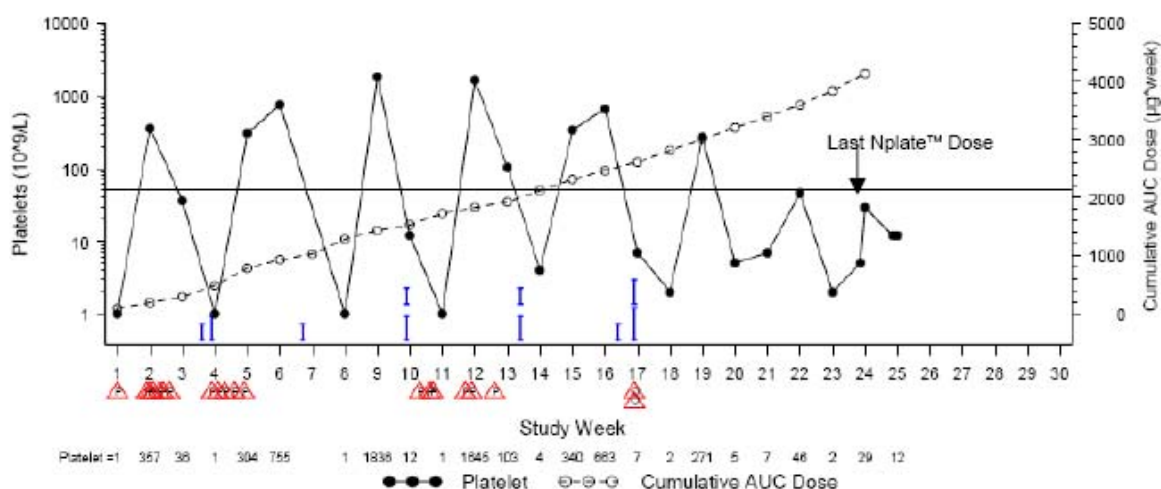


Only rescue medication use in Weeks 1-24 have been included.

Severity of bleeding event is represented by the length of the vertical line segment.

Rescue medications are indicated by the following: P=Prednisone, I=Immunoglobulins, B=Platelets, Human Blood, and O=Other.

**Figure 2: Individual platelet count and cumulative dose over time:
Non-Durable Responder**



Only rescue medication use in Weeks 1-24 have been included.
Severity of bleeding event is represented by the length of the vertical line segment.
Rescue medications are indicated by the following: P=Prednisone, I=Immunoglobulins, B=Platelets, Human Blood, and O=Other.

Immunogenicity

As with all therapeutic proteins, patients may develop antibodies to the therapeutic protein. Patients were screened for immunogenicity to romiplostim using a Biacore-based biosensor immunoassay. This assay is capable of detecting both high and low affinity binding antibodies that bind to romiplostim and cross-react with TPO. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay.

In clinical studies, the incidence of pre-existing antibodies to romiplostim was 8% (17/225) and the incidence of binding antibody development during Nplate™ treatment was 10% (23/225). The incidence of pre-existing antibodies to endogenous TPO was 5% (12/225) and the incidence of binding antibody development to endogenous TPO during Nplate™ treatment was 5% (12/225). Of the patients with positive antibodies to romiplostim or to TPO, 1 (0.4%) patient had neutralizing activity to romiplostim and none had neutralizing activity to TPO. There was no correlation of antibody activity and either clinical effectiveness or safety.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to romiplostim with the incidence of antibodies to other products may be misleading.

If formation of neutralizing antibodies is suspected, Amgen Canada Medical Information (1-866-502-6436) may be contacted for information on antibody testing.

DRUG INTERACTIONS

No formal drug-drug interaction studies of Nplate™ (romiplostim) have been performed.

ITP medical therapies used in combination with Nplate™ in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulins (IVIG), and anti-D immunoglobulin. When combining Nplate™ with other ITP medical therapies, platelet counts should be monitored in order to manage unexpected changes (see *Dosage and Administration*).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Treatment should be prescribed and monitored only by qualified healthcare providers.

Nplate™ (romiplostim) is administered subcutaneously.

Use the lowest dose of Nplate™ necessary to achieve and maintain a platelet count $\geq 50 \times 10^9/L$. Administer Nplate™ as a weekly subcutaneous (SC) injection with dose adjustments based upon the platelet count response. Nplate™ should not be used in an attempt to normalize platelet counts.

The prescribed Nplate™ dose may consist of a very small volume (for example, 0.15 mL). As the Nplate™ volume may be very small, a syringe with 0.01 mL graduations may be necessary.

Recommended Initial Dose

The recommended initial dose for Nplate™ is 1 mcg/kg based on actual body weight, administered once weekly as a subcutaneous (SC) injection. All dosing calculations should be based on actual body weight at initiation of treatment.

Dose Adjustments

Use the actual body weight at initiation of therapy, then adjust the weekly dose of Nplate™ by increments of 1 mcg/kg until the patient achieves a platelet count $\geq 50 \times 10^9/L$. Assess the platelet count weekly until a stable platelet count ($\geq 50 \times 10^9/L$ for at least 4 weeks without dose adjustment) has been achieved. Obtain platelet counts monthly thereafter. Do not exceed a maximum weekly dose of 10 mcg/kg.

Adjust the dose as follows:

- If the platelet count is $< 50 \times 10^9/L$, increase the dose by 1 mcg/kg every 1-2 weeks.
- If platelet count is $> 200 \times 10^9/L$ for 2 consecutive weeks, reduce the dose by 1 mcg/kg every 2 weeks.
- If platelet count is $> 400 \times 10^9/L$, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to $< 200 \times 10^9/L$, resume Nplate™ at a dose reduced by 1 mcg/kg.

Treatment Discontinuation

The recurrence of thrombocytopenia should be expected upon discontinuation of treatment (see *Warnings and Precautions*). Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician.

Discontinue Nplate™ if the platelet count does not increase to a level of $50 \times 10^9/L$ or to a level sufficient to avoid clinically important bleeding after four weeks at the highest weekly dose of 10 mcg/kg. Dosing requirements should be individualized according to the needs of each ITP patient. During the placebo controlled studies, 3 mcg/kg (25th-75th percentile: 1-4 mcg/kg) was the median most frequent dose administered to both splenectomized and nonsplenectomized patients to achieve a platelet count $\geq 50 \times 10^9/L$. In an open label study of refractory patients with ITP who had failed numerous prior ITP therapies, 7 mcg/kg (25th-75th percentile: 5-9.5 mcg/kg) was the median most frequent dose administered to achieve the same platelet level. Therefore, while doses higher than 7 mcg/kg are not required for most patients, a subgroup of the most severely ill patients may require higher maximum doses. Doses higher than 10 mcg/kg should not be exceeded.

Use of Nplate™ with Concomitant Medical ITP Therapies

Medical ITP therapies used in combination with Nplate™ in clinical studies included corticosteroids, danazol, azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Corticosteroids, danazol, and azathioprine were reduced or discontinued when given in combination with Nplate™ (see Clinical Studies). If the patient's platelet count is $\geq 50 \times 10^9/L$, medical ITP therapies may be reduced or discontinued.

Physician knowledge of platelet response may have had an impact on the differential reduction of concomitant medications and administration of rescue medications observed in clinical studies.

Rescue medications including platelet transfusions might be required during treatment with Nplate™.

Administration

Nplate™ should be administered by subcutaneous injection.

Reconstitution Instructions

Nplate™ is supplied in two vial presentations: 250 mcg/vial and 500 mcg/vial. Each vial contains sufficient product to provide a deliverable dose of up to 250 mcg and 500 mcg, respectively, when reconstituted as instructed. See Table 9 below.

Nplate™ (250 mcg) single-use vial (containing 375 mcg powder for solution for injection) should be reconstituted with 0.72 mL of Sterile Water for Injection USP, yielding a 500 mcg/mL concentration (total extractable dose per vial is 250 mcg in 0.5 mL).

Nplate™ (500 mcg) single-use vial (containing 625 mcg powder for solution for injection) should be reconstituted with 1.2 mL of Sterile Water for Injection USP, yielding a 500 mcg/mL concentration (total extractable dose per vial is 500 mcg in 1.0 mL).

Nplate™ should only be reconstituted with Sterile Water for Injection. Do not use saline or

bacteriostatic water when reconstituting the product. Nplate™ should be reconstituted under aseptic conditions.

Nplate™ should not be mixed with other medicinal products or given as an infusion. No other medications should be added to solutions containing Nplate™, and do not dilute Nplate™ with other diluents.

Table 9 Reconstitution of Nplate™ Single-Use Vials

Nplate™ Single-Use Vial	Total Vial Content of Nplate™		Sterile Water for Injection*	=	Deliverable Product and Volume	Final Concentration
250 mcg	375 mcg	add	0.72 mL	=	250 mcg in 0.5 mL	500 mcg/mL
500 mcg	625 mcg	add	1.2 mL	=	500 mcg in 1 mL	500 mcg/mL

*Use Sterile Water for Injection

During reconstitution, the vial contents may be gently swirled and inverted. Avoid excess or vigorous agitation: **DO NOT SHAKE**. Generally, dissolution of Nplate™ takes less than 2 minutes. The reconstituted Nplate™ solution should be clear and colorless. Visually inspect the reconstituted solution for particulate matter and/or discoloration. Do not administer Nplate™ if particulate matter and/or discoloration are observed.

Reconstituted product should be administered within 24 hours, as it does not contain a preservative. The reconstituted product can remain at room temperature (25°C/77°F) or be refrigerated at 2° to 8°C (36° to 46°F) for up to 24 hours prior to administration. The reconstituted product must be protected from light.

To determine the injection volume to be administered, first identify the patient's total dose in micrograms using the dosing information (see *Dosage and Administration*). For example, a 75 kg patient initiating therapy at 1 mcg/kg will begin with a dose of 75 mcg. Next, calculate the volume of Nplate™ solution that is given to the patient by dividing the microgram dose by the concentration of the reconstituted Nplate™ solution (500 mcg/mL). For this patient example, the 75 mcg dose is divided by 500 mcg/mL, resulting in an injection volume of 0.15 mL.

As the injection volume may be very small, use a syringe with gradations to 0.01 mL.

Discard any unused portion. Do not pool unused portions from the vials. Do not administer more than one dose from a vial.

OVERDOSAGE

In early clinical studies, the maximum dose of Nplate™ (romiplostim) was 30 mcg/kg. This was later reduced to 10 mcg/kg due to lack of additional clinical benefit of doses above this level.

No adverse effects were seen in monkeys given a single dose of 5000 mcg/kg (500 times the maximum clinical dose of 10 mcg/kg).

In the event of overdose, platelet counts may increase above the normal range. In this case, discontinue Nplate™ and monitor platelet counts. Reinitiate treatment with Nplate™ in accordance with dosing and administration recommendations

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Nplate™ (romiplostim) increases platelet production through binding and activation of the thrombopoietin receptor, a mechanism analogous to endogenous thrombopoietin (eTPO).

Pharmacodynamics

Among all ITP patients treated with Nplate™ in study S1 (212) and S2 (105), during the 24-week treatment period the mean (SD) number of weeks with platelet response (platelet count $\geq 50 \times 10^9/L$ without rescue therapy within 8 weeks) was 15 (7.5) for non-splenectomized patients and 12 (7.9) for splenectomized patients (See Table 12).

Pharmacokinetics

In the long-term extension study in patients with ITP (n=20) receiving weekly treatment of Nplate™ subcutaneously, the pharmacokinetics of Nplate™ over the dose range of 3 to 15 mcg/kg (Table 10) indicated that peak serum concentrations were observed about 7 to 50 hours postdose (median, 14 hours) with half-life values ranging from 1 to 34 days (median, 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum Nplate™ is in part dependent on the TPO receptor on platelets. As a result, for a given dose, high platelet counts in patients are associated with low serum concentrations and vice versa. The relationship between the exposure (AUC or C_{max}) and the predose platelet count was nonlinear, however, it is approximately linear in log-log scale. In another ITP clinical study, no accumulation in serum concentrations was observed after 6 weekly doses of Nplate™ (3 mcg/kg). The potential for accumulation at higher dose of Nplate™ is unknown.

Table 10: PK Parameters of Nplate™ Following 2 Consecutive Weekly Subcutaneous Doses in Subjects With ITP After Chronic Weekly Treatment in The Long-Term Extension Study

Subject	Dose mcg/kg	AUC _{0-7day}		C _{max}		t _{max}		t _{1/2}		Predose Platelet Count (x 10 ⁹ /L)	
		(pg*hr/mL)		(pg/mL)		(hour)		(hour)		(x 10 ⁹ /L)	
		Week 1	Week 2	Week 1	Week 2	Week 1	Week 2	Week 1	Week 2	Week 1	Week 2
1	3	2970	NA	37.8	NA	24	NA	47	NA	304	216
2	4	8880	9400	71.8	90.8	36	24	826	207	195	84
3	4	6240	6830	45.1	56	23	23	172	102	144	99
4	4	— ^a	—	—	—	—	—	—	—	194	131
5	4	14500	7180	289	124	12	11	24	38	124	151
6	5	18800	18900	390	338	12	12	53	131	99	94
7	5	11700	21400	192	303	8	24	183	60	131	104
8	5	10400	4830	162	52.4	12	24	145	29	102	144
9	5	5040	5090	94.3	67.2	11	24	415	51	257	326
10	7	7290	5260	105	37.1	7	24	39	153	100	333
11	8	117000	94100	1510	1310	12	11	67	91	74	74
12	8	13700	8660	197	74.2	12	36	115	127	37	115
13	8	12400	10400	149	88.5	24	24	70	125	182	214
14	10	66300	18300	1440	159	24	22	78	124	78	152
15	15	305000	209000	8580	7550	12	12	68	109	5	5

^a All samples from this subject were below the limit of quantification.

Data from 5 subjects were not included due to incomplete concentration time profile or dose change; AUC_{0-7day} = the area under the Nplate™ serum concentration-time curve over 7 days; C_{max} = the maximum serum concentration; t_{max} = the time of C_{max}; t_{1/2} = the half-life, probably represents the absorption rate due to flip-flop kinetics; NA = not available.

STORAGE AND STABILITY

Nplate™ (romiplostim) should be stored refrigerated at 2° to 8°C (36° to 46°F); the vial should be kept in the carton to protect from light until time of use. Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Nplate™ (romiplostim) is supplied as a sterile lyophilized solid white powder containing 250 mcg or 500 mcg Nplate™ in single-dose vials for reconstitution.

Each Nplate™ (250 mcg) vial contains 375 mcg romiplostim, 1.2 mg L-histidine, 30 mg mannitol, 15 mg sucrose, 0.03 mg polysorbate 20, dilute hydrochloric acid (for pH adjustment).

Each Nplate™ (500 mcg) vial contains 625 mcg romiplostim, 1.9 mg L-histidine, 50 mg mannitol, 25 mg sucrose, 0.05 mg polysorbate 20, dilute hydrochloric acid (for pH adjustment).

Each vial has a rubber stopper, an aluminum seal and a plastic flip-off cap.

Nplate™ is provided in a dispensing pack containing one vial.

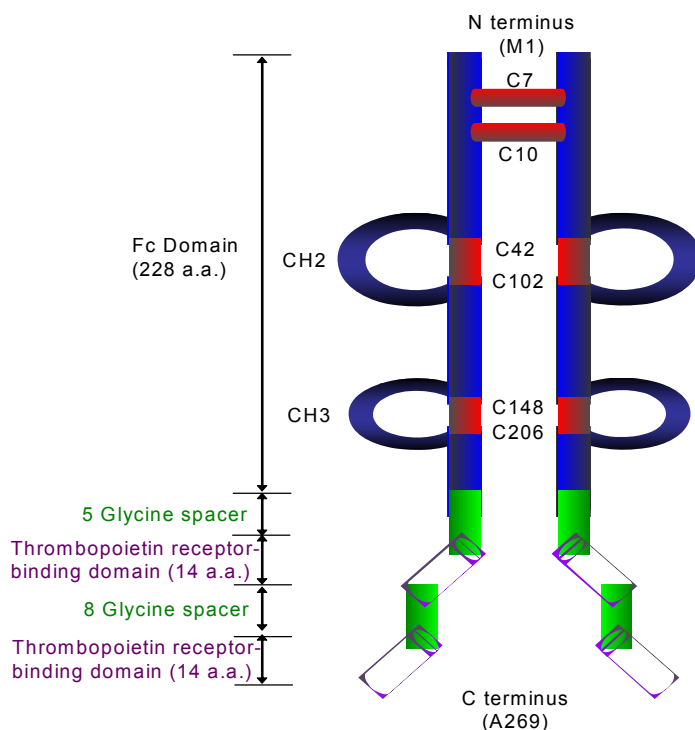
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: romiplostim

Structural formula:



CLINICAL TRIALS

Study demographics and trial design

The safety and efficacy of Nplate™ (romiplostim) were evaluated in two Phase 3 placebo-controlled, double-blind studies in adults with chronic ITP who had completed at least one treatment prior to study entry.

Study S1 (212) evaluated patients who were nonsplenectomized and had an inadequate response or were intolerant to prior therapies. Patients had a median of 3 (range, 1 to 7) treatments for ITP prior to study entry. Prior treatments included corticosteroids (90% of all patients), immunoglobulins (76%), rituximab (29%), cytotoxic therapies (21%), danazol (11%), and azathioprine (5%). Patients had a median platelet count of $19 \times 10^9/L$ at study entry.

Study S2 (105) evaluated patients who were splenectomized and continued to have thrombocytopenia. In addition to a splenectomy, patients had a median of 6 (range, 3 to 10)

treatments for ITP prior to study entry. Prior treatments included corticosteroids (98% of all patients), immunoglobulins (97%), rituximab (71%), danazol (37%), cytotoxic therapies (68%), and azathioprine (24%). Patients had a median platelet count of $14 \times 10^9/L$ at study entry.

Entry criteria were the same in both of the placebo controlled studies except that patients in study 1 had not undergone splenectomy while patients in study 2 were refractory to splenectomy. Patients were required to be at least 18 years old with a diagnosis of ITP according to American Society of Hematology (ASH) guidelines. Patients must have completed at least 1 previous treatment for ITP and had a mean of 3 platelet counts during screening and pre-treatment periods that were $\leq 30 \times 10^9/L$, with no individual count $> 35 \times 10^9/L$. At the time of study entry, patients could not be receiving any treatment for ITP except corticosteroids, azathioprine, or danazol administered at a constant dose and schedule. Hemoglobin of at least 9.0 g/dL was required at baseline, and patients over 60 years of age were required to have a documented history of chronic ITP with a bone marrow report in order to support the diagnosis. 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.

Among patients enrolled into study 2, only 16.6% (7/42) of Nplate™ treated patients and zero (0/21) placebo treated patients had undergone splenectomy within 6 months of enrollment.

A summary of the patient demographics and trial designs for the two Phase 3, placebo-controlled studies and the long-term extension study is provided in Table 11.

Table 11. Summary of Clinical Efficacy Studies (Subjects with ITP)

Study Number/ Type	Description	Primary Endpoint	Number Randomized/ Treatment	Age Range (years)	Race/Gender	Dosing Regimen
Placebo-controlled, pivotal trials						
Study S1 (212) ¹	Phase 3 double-blind, (2:1, Nplate™: placebo), safety and efficacy in subjects ≥ 18 years old, who have not undergone splenectomy; stratified by concurrent ITP therapy. Dose adjustment to maintain platelet target range of 50 to 200 x 10 ⁹ /L. At 24 weeks study drug withdrawn; subject complete at platelets ≤ 50 x10 ⁹ /L, or at week 36 with > 50 x10 ⁹ /L.	Incidence of durable platelet response, defined as achieving ≥ 6 weekly responses during last 8 weeks of treatment with no rescue medication	62 subjects: 41 Nplate™ 21 placebo	21 to 88	White, 49 Black, 4 Other, 5 Asian, 3 Native Hawaiian or Other Pacific Islander, 1 Men, 19 Women, 43	1.0 to 15 mcg/kg SC weekly, adjusted by platelet count, for 24 weeks
Study S2 (105) ²	Phase 3 double-blind, (2:1, Nplate™: placebo), safety and efficacy in subjects ≥ 18 years old, refractory to splenectomy; stratified by concurrent ITP therapy. Dose adjustment to maintain platelet target range of 50 to 200 x 10 ⁹ /L. At 24 weeks study drug withdrawn; subject complete at platelets ≤ 50 x10 ⁹ /L, or at week 36 with > 50 x10 ⁹ /L.	Incidence of durable platelet response, defined as achieving ≥ 6 weekly responses during last 8 weeks of treatment with no rescue medication	63 subjects: 42 Nplate™ 21 placebo	26 to 88	White, 53 Black, 5 Hispanic, 3 Asian, 2 Men, 25 Women, 38	1.0 to 15 mcg/kg SC weekly, adjusted by platelet count, for 24 weeks

Table 11. Summary of Clinical Efficacy Studies (Subjects with ITP)

Study Number/ Type	Description	Primary Endpoint	Number Randomized/ Treatment	Age Range (years)	Race/Gender	Dosing Regimen
Long-term extension study						
Study S3 (213)	Open-label extension study designed to assess the durability of platelet count increases in subjects previously completing a Nplate™ ITP study	Incidence of adverse events, including clinically significant changes in laboratory values and incidence of antibody formation	137 Nplate™	21 to 89	White, 113 Black, 7 Hispanic, 11 Asian, 4 Other, 2 Men, 46 Women, 91	1.0 to 30 mcg/kg SC weekly, adjusted by platelet count; Maximum dose reduced to 15 mcg/kg and then to 10 mcg/kg

Study results

Both of the placebo controlled studies were similarly designed. Patients (≥ 18 years) were randomized in a 2:1 ratio to receive a starting dose of Nplate™ 1 mcg/kg or placebo. Patients received single weekly SC injections for 24 weeks. Doses were adjusted to maintain platelet counts (50 to $200 \times 10^9/L$).

In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response (defined as weekly platelet count $\geq 50 \times 10^9/L$ for 6 or more times during last 8 weeks of treatment in the absence of rescue medication any time during the treatment period). In the placebo-controlled studies, the most frequently used weekly dose for splenectomized patients was between 2-7 mcg/kg (25th-75th percentile respectively; median 3 mcg/kg) and for nonsplenectomized patients was between 1-3 mcg/kg (25th-75th percentile respectively; median 2 mcg/kg). As shown in Table 12, treatment with Nplate™ demonstrated significant improvements compared to placebo in both clinical studies for all efficacy endpoints for all patients randomized to the studies based on an intention to treat analysis.

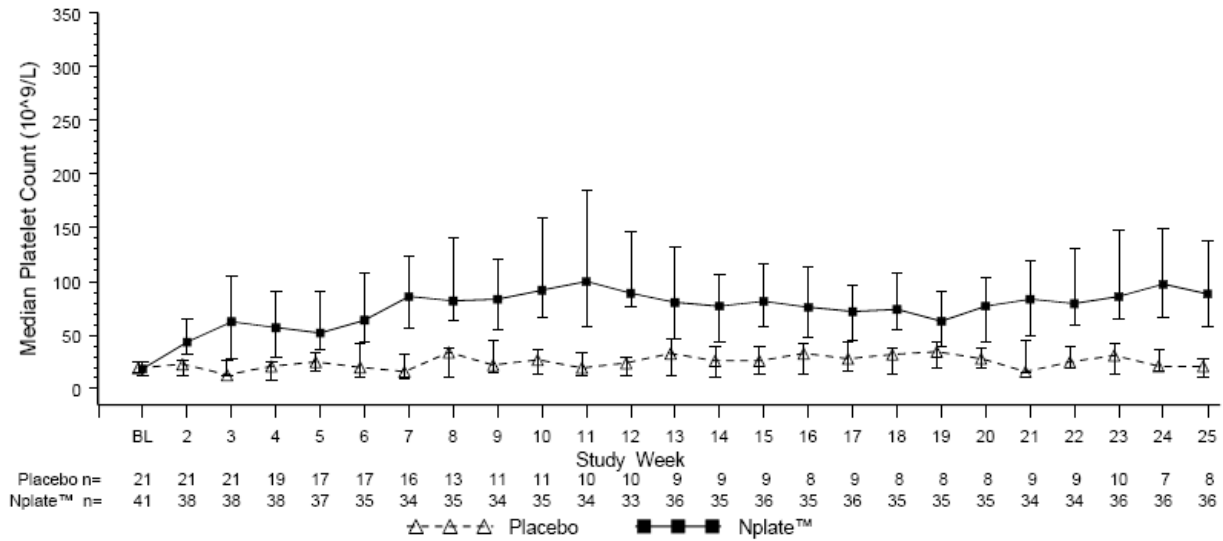
Table 12 Summary of Efficacy Results from Placebo-controlled Studies

	Study S1 (212) Nonsplenectomized Patients		Study S2 (105) Splenectomized Patients	
	Nplate™ (n = 41)	Placebo (n = 21)	Nplate™ (n = 42)	Placebo (n = 21)
No. (%) Patients with Durable Platelet Response ^a (95% CI) p-value	25 (61%) (45%, 76%) <0.0001	1 (5%) (0%, 24%)	16 (38%) (24%, 54%) 0.0013	0 (0%) (0%, 16%)
Patients with Transient Platelet Response ^b (95% CI)	11(27%) (14%, 43%)	2 (10%) (1%, 30%)	17 (41%) (26%, 57%)	0 (0%) (0%, 16%)
Mean No. Weeks with Platelet Response ^c (SD) p-value	15 7.5 <0.0001	1 3.5	12 7.9 <0.0001	0 0.5
No. (%) Patients Requiring Rescue Therapies ^d (95% CI) p-value	8 (20%) (9%, 35%) 0.001	13 (62%) (38%, 82%)	11 (26%) (14%, 42%) 0.0175	12 (57%) (34%, 78%)
No. (%) Patients with Durable Platelet Response with Stable Dose ^e (95% CI) p-value	21 (51%) (35%, 67%) 0.0001	0 (0%) (0%, 16%)	13 (31%) (18%, 47%) 0.0046	0 (0%) (0%, 16%)

- ^a Durable platelet response was defined as weekly platelet count $\geq 50 \times 10^9/L$ for 6 or more times for study weeks 18-25 in the absence of rescue medication any time during the treatment period.
- ^b Transient platelet response was defined as achieving weekly platelet response for 4 or more times between weeks 2-25 but without durable platelet response.
- ^c Number of weeks with platelet response is defined as number of weeks with platelet counts $\geq 50 \times 10^9/L$ during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medications.
- ^d Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue medications were not considered for durable platelet response. Rescue therapies allowed in the study were IVIG, platelet transfusions, anti-D immunoglobulin, and corticosteroids. Physician knowledge of platelet response may have had an impact on the differential reduction of administration of rescue medications observed in clinical studies
- ^e Stable dose defined as dose maintained within ± 1 mcg/kg during the last 8 weeks of treatment.

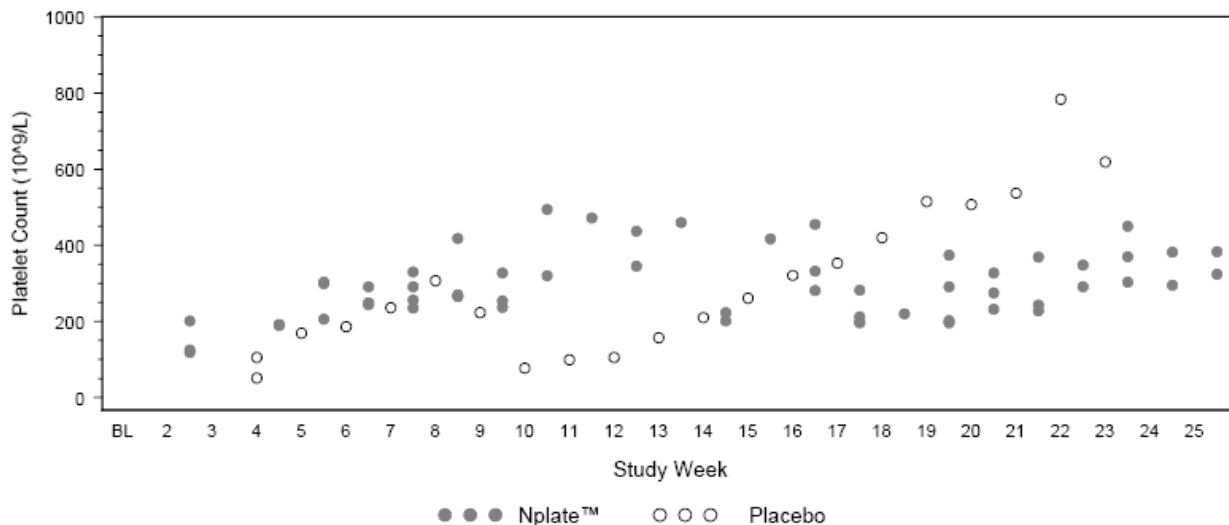
In both Phase 3, placebo-controlled studies, 50% to 70% of patients maintained platelet counts $\geq 50 \times 10^9/L$ starting week 6 during the 24-week treatment period. In the placebo group, 0% to 7% of patients were able to achieve a platelet count response during the 6 months of treatment. Figure 3, Figure 4 and Figure 5 provide median (Q1, Q3) and notched box presentations, respectively, of weekly platelet counts in Nplate™-treated nonsplenectomized subjects. Figure 6, Figure 7 and Figure 8 provide median (Q1, Q3) and notched box presentations, respectively, of weekly platelet counts in Nplate™-treated splenectomized subjects.

Figure 3: Median (Q1, Q3) Weekly Platelet Counts in Nonsplenectomized Subjects



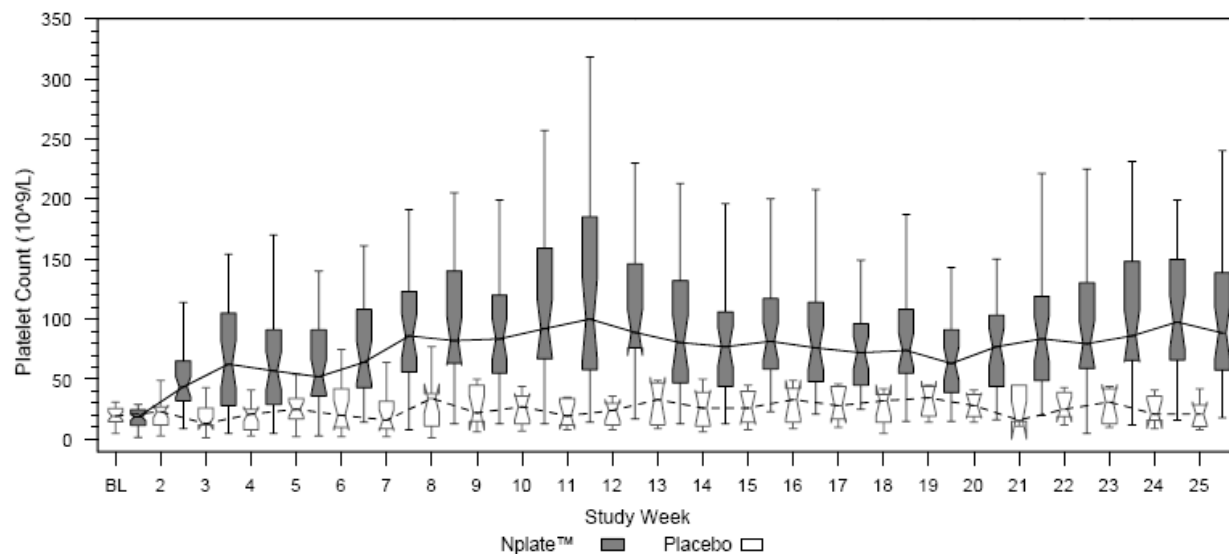
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use. Baseline platelet value (BL) = mean of platelet counts at Days -8, -2 and pre-dose Day 1.

Figure 4: Notched Box Weekly Platelet Counts in Nonsplenectomized Subjects (Outliers)



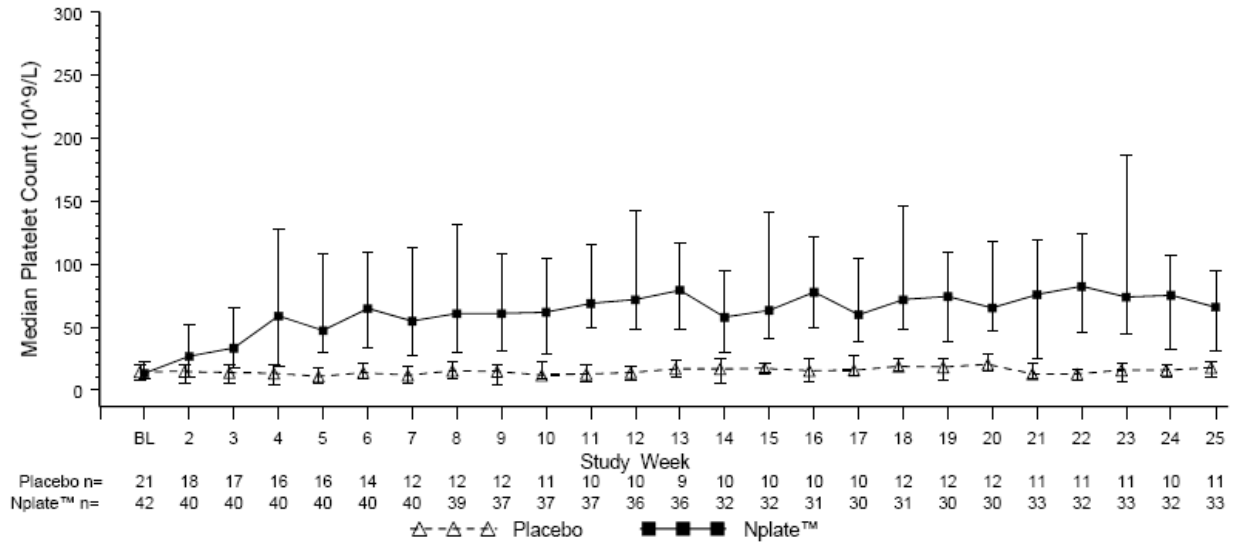
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use. Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and pre-dose day 1.

Figure 5: Notched Box Weekly Platelet Counts in Nonsplenectomized Subjects



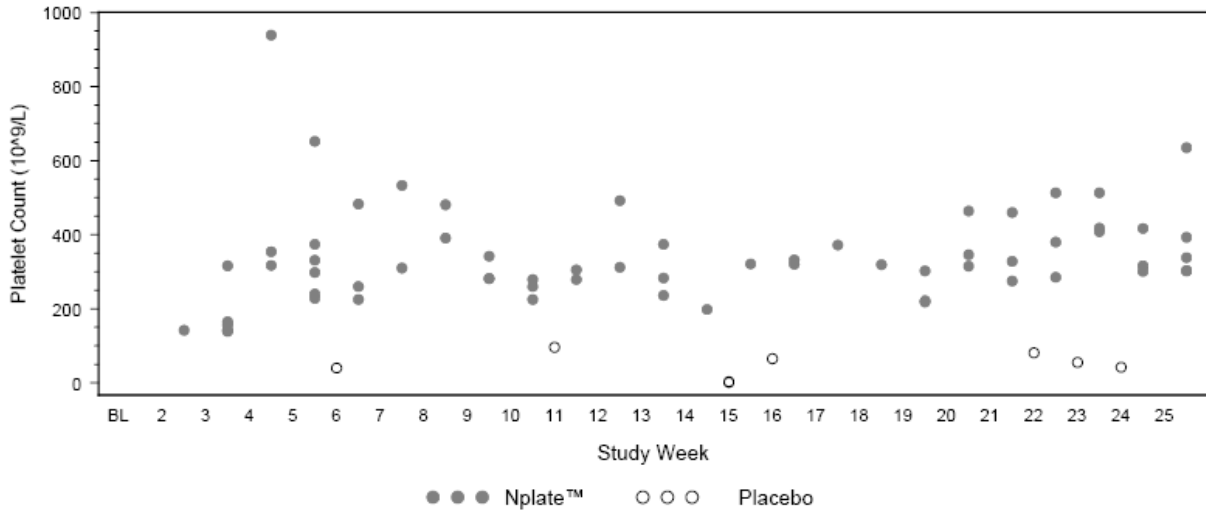
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use. Whiskers represent the upper and lower adjacent values; top and bottom of box indicate inter-quartile range. Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and pre-dose day 1.

Figure 6: Median (Q1, Q3) Weekly Platelet Counts in Splenectomized Subjects



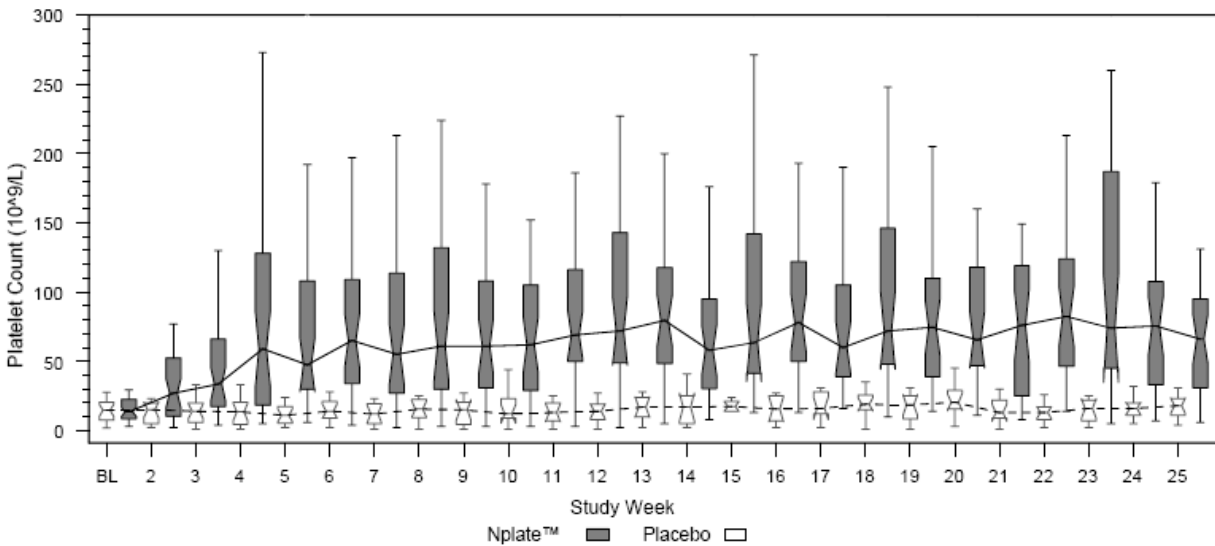
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use.
 Baseline platelet value (BL) = mean of platelet counts at Days -8, -2 and pre-dose Day 1.

Figure 7: Notched Box Weekly Platelet Counts in Splenectomized Subjects (Outliers)



Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use. Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and pre-dose day 1.

Figure 8: Notched Box Weekly Platelet Counts in Splenectomized Subjects



Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use. Whiskers represent the upper and lower adjacent values; top and bottom of box indicate inter-quartile range. Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and pre-dose day 1.

Individual subject profiles for platelet counts over time exhibit greater variability than what is shown by the median (Q1, Q3) plots, especially for patients whose platelet counts cannot be stabilised.

Nplate™ has been used alone or in combination with other ITP therapies such as corticosteroids, azathioprine, or danazol.

Splenectomized patients had a higher number of previous therapies, higher rates of use of concurrent ITP therapy at baseline, and a tendency to need higher Nplate™ doses for an initial

response. They also seemed to have more variability in response to Nplate™ than did nonsplenectomized patients.

Bleeding events in Subjects with Variable Platelet Counts (Unstable Platelet Counts)

Nine (7%) subjects in the pivotal studies had platelet counts that rose and fell to extreme levels within short periods of time; these subjects' course on study often included multiple rescue medications and numerous Nplate™ dose adjustments. In an effort to quantify and characterize these subjects, a definition was retrospectively developed for Variable Platelet Count Subject. This was any subject who had 5 or more fluctuations during the 25-week treatment period of a platelet count that either increased or decreased by $> 100 \times 10^9/L$ within a single week while also crossing $50 \times 10^9/L$. (See *Clinical Trials Adverse Drug Reactions, Bleeding Events in Subjects with Variable Platelet Counts (Unstable Platelet Counts)*).

Discontinuation of Concurrent ITP Medical Therapies

In both Phase 3, placebo-controlled, double-blind studies, patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the study (i.e. corticosteroids, danazol, and/or azathioprine). Twenty-one nonsplenectomized and 18 splenectomized patients received concurrent ITP medical treatments (primarily corticosteroids) at the start of study. Sixty-seven percent of splenectomized patients who were receiving Nplate™ were able to discontinue the concurrent ITP medical therapies by the end of the treatment period, while 36% of nonsplenectomized patients receiving Nplate™ were able to discontinue concurrent ITP treatment. Table 13 describes the number of Phase 3 study patients who were able to discontinue baseline ITP therapies by week 25 (end of treatment), for Study S1 (212), Study S2 (105).

Table 13. Concurrent ITP Medical Therapies

	Study 1 Nonsplenectomized Patients		Study 2 Splenectomized Patients	
	Nplate™ (n = 41)	Placebo (n = 21)	Nplate™ (n = 42)	Placebo (n = 21)
No. of Patients receiving Baseline Concurrent ITP Medical Therapies	11	10	12	6
At Week 25, No. (%) of Patients who Discontinued^{a, b, c,}	4 (36%)	3 (30%)	8 (67%)	0 (0%)

^a Percentage was calculated based on number of patients with baseline concurrent ITP therapy.

^b If a patient withdrew from study early, the last record of the baseline concurrent ITP medicine was used.

^c For multiple baseline concurrent ITP therapies, all therapies must have been discontinued.

Physician knowledge of platelet response may have had an impact on the differential reduction of concomitant medications observed in clinical studies.

Use of Rescue Therapies

Rescue therapies (ie, corticosteroids, IVIG, platelet transfusions, anti-D immunoglobulin) were permitted at the discretion of the treating physician for bleeding, wet purpura, or if the patient was at immediate risk. The total incidence of rescue therapy use was considerably higher for patients treated with placebo than with Nplate™ in both the splenectomized and nonsplenectomized patients (see Table 14 and Table 15).

Table 14: Subject Incidence of Rescue Medications (Nonsplenectomized)

	Nplate™ (N =41) n (%)	Placebo (N =21) n (%)
Subjects receiving rescue medications	8 (19.5)	13 (61.9)
ANTI-D IMMUNOGLOBULIN	0 (0.0)	1 (4.8)
CYCLOSPORIN ^a	1 (2.4)	0 (0.0)
DEXAMETHASONE	3 (7.3)	1 (4.8)
IMMUNOGLOBULIN HUMAN ANTI-RH	2 (4.9)	3 (14.3)
IMMUNOGLOBULIN HUMAN NORMAL	1 (2.4)	4 (19.0)
IMMUNOGLOBULINS	3 (7.3)	3 (14.3)
METHYLPREDNISOLONE	1 (2.4)	0 (0.0)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (2.4)	1 (4.8)
PLATELETS, HUMAN BLOOD	1 (2.4)	2 (9.5)
PREDNISON	3 (7.3)	4 (19.0)
RITUXIMAB ^a	0 (0.0)	1 (4.8)

^a Protocol deviations – Cyclosporin and Rituximab were not permitted rescue medications per protocol. Full analysis set includes all randomized subjects.

Percentages are based on full analysis set.

Rescue medication was defined as any medication that was administered for the intended purpose of raising platelet count.

Rescue medication uses during the 24 weeks treatment period were counted.

Table 15 Subject Incidence of Rescue Medications (Splenectomized)

	Nplate™ (N=42)	Placebo (N =21)
	n (%)	n (%)
Subjects receiving rescue medications	11 (26.2)	12 (57.1)
AZATHIOPRINE	0 (0.0)	1 (4.8)
BLOOD TRANSFUSION, AUXILIARY PRODUCTS	1 (2.4)	0 (0.0)
DEXAMETHASONE	1 (2.4)	2 (9.5)
IMMUNOGLOBULIN HUMAN NORMAL	2 (4.8)	2 (9.5)
IMMUNOGLOBULINS	5 (11.9)	9 (42.9)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (2.4)	1 (4.8)
PLATELETS, HUMAN BLOOD	4 (9.5)	4 (19.0)
PREDNISOLONE SODIUM SULFOBENZOATE	1 (2.4)	0 (0.0)
PREDNISONE	4 (9.5)	5 (23.8)

Full analysis set and percentages are based on randomized subjects.

Rescue medication was defined as any medication that was administered for the intended purpose of raising platelet count.

Rescue medication uses during the 24 weeks treatment period were counted.

Physician knowledge of platelet response may have had an impact on the differential reduction of concomitant medications and administration of rescue medications observed in clinical studies.

Long-term ITP Extension Study

Subjects who had completed a previous Nplate™ ITP study (including the Phase 3 studies) were allowed to enroll in a long-term open label extension study. Nplate™ was administered once weekly either at the same dose received in the previous study (for subjects who had received Nplate™ in a previous study) or at a starting dose of 1 µg/kg (for subjects who had received placebo in the previous study).

Subjects in the long-term extension continued with weekly dosing and individual dose adjustments of Nplate™ based on platelet counts. Physicians evaluated subjects who responded and had been on a stable dose for at least 3 weeks for self-administration of Nplate™. Those subjects who demonstrated the ability to administer Nplate™ under clinical supervision were allowed to self-administer at the physician's discretion and continued to be monitored on a monthly basis.

One hundred and thirty seven subjects who completed their parent study were enrolled in the extension study 20030213, and 136 subjects received at least 1 dose of Nplate™. For this interim analysis, the 136 subjects had been on treatment for a median of 39 weeks (range, 1 week to 122 weeks).

For this interim analysis, a platelet response (doubling of baseline platelet count and platelet count $\geq 50 \times 10^9/L$ at any time on study in the absence of rescue medication within 8 weeks) was achieved in 82% of subjects (95% CI: 75%, 88%). One week after the first dose of Nplate™ (ie, at week 2), the proportion of subjects with platelet responses was 31%. Kaplan-Meier analysis of time to first platelet response was 2 weeks (95% CI: 2, 3) for the 50th

percentile (median) and 7 weeks (95% CI: 5, 11) for the 75th percentile. The median Nplate™ dose prior to first platelet response was 3 µg/kg (range, 1 to 18 µg/kg).

The overall subject incidence of rescue medication use was 34.6%.

In conclusion, 31% of subjects responded positively in the first week after treatment and, from the fourth week onward, responses were in the range of 52% to 73%. Due to the heterogeneity of the population with regard to inclusion criteria, disease baseline characteristics, treatment history, concurrent medication, Nplate™ dose received and length of treatment included in this study, data on the long-term efficacy and safety of Nplate™ should be interpreted with caution.

DETAILED PHARMACOLOGY

Pharmacodynamics

Nplate™ (romiplostim) increases platelet production through binding and activation of the thrombopoietin receptor, which signals and activates intracellular transcriptional pathways; a mechanism analogous to endogenous thrombopoietin (eTPO). Nplate™ has no amino acid sequence homology to eTPO.

TOXICOLOGY

Carcinogenesis, Mutagenesis

The carcinogenic potential of Nplate™ (romiplostim) has not been evaluated. The mutagenic potential of Nplate™ has not been evaluated.

Impairment of Fertility

Nplate™ had no observed effect on the fertility of rats at doses ranging from 6- to 10-fold higher than the highest anticipated clinical dose.

Reproductive Toxicology

Developmental toxicity studies have been performed in rodents and rabbits at doses ranging from 6- to 10-fold higher than the highest anticipated clinical dose and have revealed no evidence of harm to the developing fetus due to Nplate™ (See Table 16).

In embryo-fetal development studies in mice, rats, and rabbits, doses ranging from 6- to 10-fold higher than the highest anticipated clinical dose were associated with reductions in maternal body weight only in mice. In mice there was evidence of increased post-implantation loss. In a prenatal and postnatal development study in rats there was a slight increase in the incidence of peri-natal pup mortality (at 10-fold higher than the highest anticipated clinical dose).

Nplate™ is known to cross the placental barrier in rats and may be transmitted from the mother to the developing fetus.

Animal Toxicology and/or Pharmacology

In a 4-week repeat dose toxicity study in rats, Nplate™ caused bone hyperostosis and marrow fibrosis at clinically equivalent and higher doses. In these studies, this finding was not observed in animals after a 4-week post-treatment recovery period (See Table 16). Studies of long-term treatment with Nplate™ in rats have not been conducted; therefore, it is not known if the fibrosis of the bone marrow is reversible in rats after long-term treatment.

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
Single-dose Studies			
Single-dose Acute Study in Sprague-Dawley Rats	Sprague-Dawley rats n = 20 (5/group): 0, 100, 300, 1000 mcg/kg SC	Single dose (day 1); necropsy on day 16	Nplate™ was generally well tolerated but appeared to cause a slightly lower body weight gain at all dose levels in female rats. One rat in the 100-mcg/kg group was found dead shortly after blood collection on day 9. No gross necropsy findings were related to Nplate™. Several clinical pathologic effects were noted at all dose levels; microscopic findings were noted in the 300-mcg/kg and 1000-mcg/kg groups, but were consistent with pharmacologic activity of Nplate™ and were not considered untoward.
Repeated-dose Studies			
Four-week Subcutaneous or Intravenous Toxicity and Toxicokinetic Study With Nplate™ in Rats With a 4-week Recovery Period	CD rats n = 130 (65/sex and 10 or 15/sex/group, as indicated in Design column): 0, 10, 30, 100 mcg/kg SC; 100 mcg/kg IV; TIW x 4 wk Additional 12/sex/group used in TK evaluations Additional 20/sex/group used in platelet aggregation	10/sex/group necropsied after 1 month treatment 5/sex/group (0 and 100 mcg/kg groups only) necropsied after 1 month treatment and 1 month recovery	Deaths occurred in all dose groups, but were more frequent in the 100-mcg/kg group. PD responses were similar between the SC and IV high-dose groups. Six animals in satellite groups, which had more handling and more associated bleeds, died. Deaths occurred approximately 2 weeks into the study, the time at which peak platelet counts would have been achieved. Platelet counts for animals that died in 100-mcg/kg groups, both IV and SC, were 3 to 4 times normal platelet counts. Four rats in the high-dose groups had evidence of exaggerated pharmacology with extramedullary hematopoiesis, megakaryocyte hyperplasia, and megakaryocytosis in lungs, liver, or spleen, or in all 3 of these organs. Femoral and sternal bone hyperostosis and marrow myelofibrosis were observed in animals necropsied at the end of treatment. Femoral and sternal bone and bone marrow were unremarkable after the recovery

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
	studies		period. Rats treated with Nplate™ exhibited 2- to 4-fold increases in platelet counts on day 10. All Nplate™-related changes were reversed or absent in the recovery period rats. Platelet aggregation was unaffected by Nplate™.
Four-week Toxicity Study of Nplate™ Administered by Subcutaneous or Intravenous Injection to Rhesus Monkeys, With a 4-week Recovery Period	Rhesus monkeys n = 38 (19/sex and 3 or 5/sex/group, as indicated in the Design column): 0 mcg/kg (IV and SC); 500, 1000 mcg/kg (SC); 5000 mcg/kg (IV and SC); TIW x 4 wk	3/sex/group necropsied after 1 month treatment 2/sex/group (0 mcg/kg and 5000 mcg/kg SC groups only) necropsied after 1 month treatment and 1 month recovery	No monkeys died during the study. No changes were observed in body weight, ocular, ECG, or urinary analyses. Nplate™-related hematologic changes were analogous to those observed in previous studies of related compounds in rhesus monkeys and reflected activity of Nplate™. All monkeys treated with Nplate™ had dose-dependent increases in platelet counts. Non-dose-dependent decreases in MPV were observed from day 14. Microscopic examination of platelets in PB smears revealed large platelets on day 14 in all monkeys receiving Nplate™ and on day 28 in most monkeys receiving Nplate™. Platelet counts and MPV returned to BL during recovery phase. Secondary to increases in platelet counts: decreases in RBC indices; increases in serum LDH, megakaryocytes in BM, and platelet aggregation. Treatment was associated with increased mononuclear cell infiltration at injection site. All Nplate™-related changes were reversed or absent after recovery. In monkeys that received Nplate™, ovarian follicular cysts were observed at a higher frequency than expected. Ovarian lesions were judged most likely a result of physiologic or developmental influences but relationship to Nplate™ could not be excluded.

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
<p>Four-week Repeated Dose Toxicity Study of Subcutaneous Nplate™ Administered to Female Cynomolgus and Rhesus Monkeys Followed by a 4-week Recovery Period</p>	<p>Female cynomolgus monkeys n = 32 (6 or 8 F/group, as indicated in Design column): 0, 100, 300, 500, 5000 mcg/kg SC; TIW x 4 wk Female rhesus monkeys n = 16 (8F/group): 0, 5000 mcg/kg SC; TIW x 4 wk</p>	<p>4/group necropsied after 1 month treatment (exception = n of 5 for the 5000-mcg/kg group); 2/group necropsied after 1 month treatment and 1 month recovery (exception = n of 3 for the 5000-mcg/kg group) 5/group necropsied after 1 month treatment; 3/group necropsied after 1 month treatment and 1 month recovery</p>	<p>In ovaries: graafian follicles, secondary follicles, corpus luteum, and vacuolated corpus luteum were observed both in the control groups and in the groups receiving Nplate™ and were the result of normal physiologic cycling. One monkey in the 100-mcg/kg group had a teratoma in the left ovary; the finding was incidental and unrelated to Nplate™ treatment. No other changes of any toxicologic significance were observed.</p>
<p>Three- and 6-Month Toxicology Study of Repeated Administration of Subcutaneous Nplate™ in Cynomolgus Monkeys</p>	<p>Cynomolgus monkeys n = 64 (8/sex/group): 0, 500, 1000, 5000 mcg/kg SC; QW x 3 or 6 mo</p>	<p>3/sex/group necropsied at week 13 3/sex/group necropsied at week 26 2/sex/group necropsied at week 34</p>	<p>No animals died during the study. No Nplate™-related clinical observations or changes in body weights, food consumption, ECG, or ophthalmology were noted. Nplate™ produced clear thrombocytosis in PB, megakaryopoiesis in BM in the 1000- and 5000-mcg/kg groups, and megakaryocytosis in the submandibular lymph nodes in the 1000-mcg/kg group. Platelet counts were increased up to approximately 4-fold over BL and MPV was decreased. Findings were consistent with action of Nplate™. Mild perivascular mononuclear cell infiltration was observed at injection sites. NOAEL of Nplate™ was 5000 mcg/kg in this study. TK of Nplate™ was linear with dose in the range of 500 to 5000 mcg/kg</p>

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
			and was similar in both male and female animals. No appreciable accumulation was observed with QW dosing for up to 26 weeks.
Reproductive and Developmental Toxicity Studies			
Fertility Study of Subcutaneous Nplate™ in Sprague-Dawley Rats	Sprague-Dawley rats n = 240 (30/sex/group): 0, 10, 30, 100 mcg/kg SC; TIW	Male rats: dosed beginning 4 weeks before cohabitation until the day before necropsy; necropsied after completion of necropsy of all female rats Female rats: dosed beginning 2 weeks before cohabitation until day before necropsy; necropsied on GD14 to 16 or 14 to 16 days after end of cohabitation	Mean body weights, body weight gains, and food consumption were lower in the 30- and 100-mcg/kg groups. All Nplate™-treated male rats had higher platelet counts than control rats, and platelet counts for female rats were increased in the 30- and 100-mcg/kg groups. Enlarged spleens were observed in the 30- and 100-mcg/kg groups. Treatment with Nplate™ had no effect on fertility. The lowest observable adverse effect level was 30 mcg/kg due to effects on body weight and food consumption. The NOAEL was 10 mcg/kg.
Study to Determine the Effects of Subcutaneous Administration of Nplate™ on Embryo-fetal Development in Mice	CD-1 mice (mated females) n = 40 (8F/group): 0, 3, 10, 30, 100 mcg/kg SC	Dosed on GD6, 9, 12, and 15 Euthanized on GD18	No mice died. Overall maternal body weight gains were reduced by 9% in the 100-mcg/kg group compared with the control group for days 0 to 18. The greatest weight gain decrease, 53.8% relative to control animals, occurred during GD 6 to 9 in the 100-mcg/kg group. Maternal body weights and body weight gains were unaffected by doses up to 30 mcg/kg. Seven to 8 pregnant females had ≥ 1 live fetus per dose group. The number of resorptions increased in the 3.0- and 100-mcg/kg

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
			groups (1.5- and 2.3-fold, respectively, versus controls). Most resorptions were early resorptions. Average live litter size was reduced in the 100-mcg/kg group by 16% compared with controls. All placenta appeared to be normal. Dose-dependent increases in platelet counts were observed. The maternal and development NOAEL was 30 mcg/kg.
A Dose Range-finding Study to Determine the Effects of Subcutaneous Administration of AMP2 on Embryo-fetal Development and Placental Transfer in Sprague Dawley Rats	Sprague-Dawley rats (mated females) n =25 (5F/group): 0, 10, 30, 60, 100 mcg/kg SC Additional 15F/group (0, 10, 30, 100 mcg/kg) for TK and antibody evaluations	Dosed on GD7, 9, 11, 13, 15, 17, and 19 Euthanized on GD22	Nplate™ had no observed effect on maternal mortality, clinical observations, maternal body weight, food consumption, gross pathology, pregnancy status, gravid uterine weight, number of corpora lutea, number and type of implantations, fetal sex, fetal body weights, or fetal external examination results. Dose-related concentrations of Nplate™ were obtained in maternal blood, fetal blood, and amniotic fluid. Nplate™ caused increases in maternal and fetal platelet counts. The NOAEL for fetuses and dams was 100 mcg/kg.
Study to Determine the Effects of Subcutaneous Administration of Nplate™ on Embryo-fetal Development in Sprague-Dawley Rats	Sprague-Dawley rats (mated females) n = 100 (25F/group): 0, 10, 30, 100 mcg/kg SC	Dosed on GD7, 9, 11, 13, 15, 17, and 19 Euthanized on GD22	Treatment with Nplate™ had no effect on maternal mortality, clinical observations, maternal body weight, food consumption, gross pathology, pregnancy status, gravid uterine weight, number of corpora lutea, number and type of implantations, fetal sex, or fetal body weight. No Nplate™-related fetal external, soft tissue, or skeletal abnormalities were noted. NOAEL for fetuses and dams was 100 mcg/kg.
Embryo-fetal Development Study of AMG Nplate™ 531 in New Zealand White Rabbits	New Zealand White rabbits (mated females)	Dosed on GD7, 9, 11, 13, 15, 17, and 19	Treatment with Nplate™ had no effect on maternal mortality, clinical observations, maternal body weight, gross pathology, pregnancy status, gravid

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
	<p>n = 25 (5F/group): 0, 10, 30, 60, 100 mcg/kg SC</p> <p>Additional 3F/group (0, 10, 30, 100 mcg/kg) used for TK evaluation</p>	<p>Euthanized on GD30</p>	<p>uterine weight, number of corpora lutea, number and type of implantations, fetal sex, fetal body weights, and fetal external examination results. The total body weight change adjusted for gravid uterine weight was statistically significantly lower in the 100-mcg/kg group than in control animals. Mean food consumption was sporadically lower in the 100-mcg/kg group. One fetus in the 100-mcg/kg group was malformed (gastroschisis, ectrodactyly, cutis aplasia), but the malformations were not related to Nplate™. Platelet counts increased 1- to 1.5-fold over controls for dams and 0.8- to 1.9-fold for fetuses. The overall incidences of development of antibodies were 44.4% for anti-Nplate™ antibodies and 0% for anti-TPO antibodies. No accumulation was observed with every-other-day multiple dosing in pregnant rabbits. Approximately dose-proportional increases in both C_{max} and AUC were observed in dams.</p>
<p>Study of the Prenatal and Postnatal Development and Maternal Function in Rats After Subcutaneous Injection of Nplate™</p>	<p>Sprague-Dawley rats (females)</p> <p>n = 176 (44/group): 0, 10, 30, 100 mcg/kg SC</p>	<p>Dosed every other day beginning GD6 to PND 20 or 21</p> <p>F1 generation assessed for functional behavior and mating function</p>	<p>Four F₀ females died at the end of the postnatal period. The deaths of 3 of these animals occurred shortly after blood collection, and the fourth animal was found dead on the day after blood collection. Because all of these females had increased platelet counts (3- to 5-fold versus controls), it is possible that the deaths were a result of an event (stress due to repeated handling and blood collections) in association with extreme thrombocytosis and increased blood viscosity. No other notable effects on clinical signs, body weights, or food consumption were observed. Mean platelet count for F₀ females that did not develop anti- Nplate™ antibodies was approximately 4-fold higher than</p>

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
			<p>mean platelet count for the controls. Mean platelet count for females that developed anti- Nplate™ neutralizing antibodies was similar to that for the controls. Of the females receiving Nplate™, 67% to 79% developed anti- Nplate™ antibodies.</p> <p>The mean length of gestation was slightly increased in females receiving Nplate™ at all dose levels (22 days) relative to the mean length of gestation in the controls (21 days). The live-birth index was decreased for females in the 100-mcg/kg/day group (92.7% to 95% versus 99% in the control group) and the percentage of stillborn pups was increased (4% to 7.3% versus 0.5% in the control group). Live litter size and pup viability after PND1 were not notably affected. There were no Nplate™-related changes in morphology or behavior of the offspring and no notable differences in the various measures of physical and functional development, up to sexual maturity, including fertility and general reproductive function.</p> <p>Splenic enlargement was noted in the majority of F₀ females in the 100-mcg/kg group and in a single F₀ female in the 30-mcg/kg group. No other differences were noted in the necropsy observations or reproductive organ weights that were related to treatment with Nplate™.</p> <p>Slight prolongation of gestation was observed for F₀ females in all Nplate™ groups. There was no definitive NOAEL for effects of Nplate™ on F₀</p>

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
			<p>gestation in this study. Based on the slightly increased perinatal pup mortality in the 100-mcg/kg group, NOAEL for prenatal and postnatal physical and functional development of the F₁ offspring was determined to be 30 mcg/kg.</p>
<p>Other Studies – Safety Pharmacology</p>			
<p>Study of the Pharmacologic Effects of a Single SC Dose of Nplate™ on Central Nervous System of Sprague-Dawley Rats</p>	<p>Sprague-Dawley rats n = 64 (8/sex/group) assigned to main toxicology study n = 16 (2/sex/group) assigned to TK study 0, 10, 30, 100 mcg/kg SC</p>	<p>Functional observation battery before administration of Nplate™ and then 12 and 48 hours and 8 days after administration of Nplate™ Blood samples taken at selected time points for TK analysis</p>	<p>No deaths occurred on study. No changes related to Nplate™ were noted during the functional observation battery. No effect was seen on body temperature or motor activity. In the 10-mcg/kg group, the concentration of Nplate™ was below the LLOQ. Due to limited sampling, TK profiles were not well characterized in this study.</p>
<p>Cardiovascular Evaluation of AMP2 in Cynomolgus Monkeys Via Bolus Intravenous Injection</p>	<p>Cynomolgus monkeys n = 12 (3M/group): 0, 500, 1000, 5000 mcg/kg IV</p>	<p>Single dose; no necropsy done</p>	<p>No adverse clinical signs, body weight changes, or changes in cardiovascular parameters occurred that were attributed to Nplate™. Platelet counts increased 1.8-, 1.6-, and 2.5-fold over BL for the 500-, 1000-, and 5000-mcg/kg groups, respectively. The platelet counts for the 5000-mcg/kg group differed significantly ($p \leq 0.01$) from control values on study days 7 and 10. No changes in blood pressure, heart rate, or body temperature could be attributed to Nplate™. No alteration was seen in ECG morphology, rhythm, or ECG intervals that could be attributed to Nplate™.</p>

Table 16: Summary of Toxicology Studies with Nplate™

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
Other Studies – Tissue Cross-reactivity			
Preliminary Studies of AMP2 Cross-Reactivity Testing on Selected Human and Cynomolgus Monkey Tissues and a Human Megakaryoblastic Cell Line	Human tissue, monkey tissue, and cultured cells 1 to 50 mcg/mL	In vitro	The results of extensive testing indicated that the immunohistochemical methods available were not sufficient to allow detection of binding of the FITC-Nplate™ ligand to its receptor on either human or cynomolgus monkey tissues or cultured cells.
Other Studies – Immunogenicity			
Induction of Anti-AMP2 Antibodies in Mice	BDF ₁ Mice n = 315 Females For doses, see Design section	Antibody and platelet measurements were obtained in the following experiments Doses of 0, 50, 100 mcg/kg SC given approximately every 21 days for 4 cycles Single SC administration at 50 mcg/kg Doses of 50, 100, 500, 1000 mcg/kg SC were administered approximately every 21 days for 6 cycles after the initial dose of 50 mcg/kg SC	Mice generated antibodies that bound Nplate™ within 1 to 2 weeks of a single exposure. The strongest serum interactions were to Thrombopoietin Mimetic Peptide. Platelet counts were increased in Nplate™-treated mice after the first cycle. From studies of subsequent exposure to Nplate™, efficacy to lower doses of Nplate™ was reduced. Mice did not develop thrombocytopenia. Dose-escalation was an effective strategy to overcoming the antibody response and did not lead to any unforeseen circumstances.

REFERENCES

1. Amgen Study 20030212: A Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy (S1)
2. Amgen Study 20030105: A Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Refractory to Splenectomy (S2)
3. Amgen Study 20030213: An Open Label Study Evaluating the Safety and Efficacy of Long-Term Dosing of AMG 531 in Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) (S3)
4. Silverstein MD, Heit JA; Mohr DN, et al. Trends in the Incidence of Deep Vein Thrombosis and Pulmonary Embolism: A 25-Year Population-Based Study. *Arch Intern Med.* 1998;158:585-593.

PART III: CONSUMER INFORMATIONPr **Nplate™**

(romiplostim)

This leaflet is part III of a three-part "Product Monograph" published when Nplate™ (romiplostim) was authorized for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Nplate™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATIONWhat the medication is used for:

Nplate™ is a protein used to treat low platelet counts in patients with immune (idiopathic) thrombocytopenic purpura (called ITP). ITP is a disease in which the immune system of your body destroys your platelets.

Platelets are the cells in your blood that help seal cuts and form blood clots. If you have too few platelets you could bruise easily and bleed for a long time after being injured. If your platelet count is very low, you may be at risk of serious, life-threatening bleeding events.

What it does:

Your doctor has given you Nplate™ to stimulate your bone marrow (part of the bone which makes blood cells) to produce more platelets. This should help to prevent bruising and bleeding.

When it should not be used:

DO NOT use Nplate™:

- if you are allergic (hypersensitive) to romiplostim or any of the other ingredients of Nplate™.
- if you are allergic to other products that are produced by DNA technology using the micro-organism *E. coli*.

What the medicinal ingredient is:

The medicinal ingredient in Nplate™ is romiplostim.

What the important nonmedicinal ingredients are:

The other ingredients are L-histidine, mannitol (E421), sucrose, polysorbate 20 and diluted hydrochloric acid.

What dosage forms it comes in:

Nplate™ is a white powder for solution for injection, available in a vial.

Each pack contains 1 vial of either 500 micrograms or 250 micrograms of powder for solution for injection.

WARNINGS AND PRECAUTIONS

- Nplate™ is not for use in patients, outside of a clinical research study, with blood cancer or a precancerous condition called myelodysplastic syndrome (MDS). If you have one of these conditions, Nplate™ may worsen your cancer or condition and may cause you to die sooner.
- Despite ongoing treatment with Nplate™, serious bleeding could occur and patients should be closely monitored during treatment. Rescue medications including platelet transfusions might be required, especially for patients with unstable platelet counts.
- When you stop receiving Nplate™, your low blood platelet counts (thrombocytopenia) may become worse than before you started Nplate™. This may result in serious life-threatening or fatal bleeding.

Treatment should be prescribed and monitored only by qualified healthcare providers.

Nplate™ should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.

Nplate™ should not be used in an attempt to normalize platelet counts.

BEFORE you use Nplate™ talk to your doctor or pharmacist if:

- you are taking or have recently taken any other medicines, including medicines obtained without a prescription
- you are pregnant; think you may be pregnant; or plan to get pregnant. Nplate™ has not been tested in pregnant women.

Care should be taken if you are breast-feeding, as it is not known whether Nplate™ is present in human milk.

Long-term use of Nplate™ may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called "increased reticulatin." It is not known if this may progress to a more severe form called "fibrosis." The mild form may cause no problems while the severe form may cause life-threatening blood problems. Signs of bone marrow changes may show up as abnormalities in your blood tests. Your healthcare provider

will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate™.

If your platelet counts have not improved after a few weeks of treatment with Nplate™, your doctor may decide to conduct more blood tests. It is also possible that your doctor may decide to stop your treatment because your bleeding condition has not improved.

Low blood platelet counts (thrombocytopenia) are likely to recur if you stop taking Nplate™. Your blood tests including platelet counts will have to be monitored, and your doctor will discuss appropriate precautions with you.

Very high blood platelet counts may increase the risk of blood clotting. Your doctor will adjust your dose of Nplate™ to ensure that your platelet count does not become too high.

Nplate™ is for use in adults aged 18 and over.

INTERACTIONS WITH THIS MEDICATION

Drug interactions between Nplate™ and other drugs have not been studied.

You should discuss with your doctor any medications you are taking before using Nplate™.

PROPER USE OF THIS MEDICATION

Treatment should be prescribed and monitored only by qualified healthcare providers.

Nplate™ is administered as an injection under the skin (subcutaneous).

Initial dose:

Your initial dose is 1 microgram of Nplate™ per kilogram of your body weight once a week.

Your doctor will tell you how much you must take. Nplate™ is intended to be injected once per week in order to keep your platelet counts up.

Your doctor will take regular blood samples to measure how your platelets are responding and may adjust your dose as necessary.

Once your platelet count is under control, your doctor will continue to regularly check your blood. Your dose may be adjusted further in order to maintain long-term control of your platelet count.

Overdose:

Nplate™ is a highly potent drug, administered at a low volume dose. Therefore, there is a potential risk of incorrect volume being administered.

If you have been given more Nplate™ than you should receive, please contact your healthcare provider immediately.

The sign of the Nplate™ overdose may be an increase in platelet count, which may be higher than the normal range. Your healthcare provider may conduct additional blood tests to monitor your platelet count, and adjust your Nplate™ dose.

Missed Dose:

If you have missed a dose of Nplate™, your doctor will discuss with you when you should have your next dose.

If you stop using Nplate™

If you stop using Nplate™ your low blood platelet count (thrombocytopenia) is likely to recur. Also, if you are taking medicines which prevent blood clots (anticoagulants or antiplatelet therapy) there is a greater risk of fatal and serious bleeding. Contact your doctor immediately as rescue medication and close monitoring could be required.

Reconstitution of Nplate™

Nplate™ is a sterile but unpreserved product and is intended for single use only.

Nplate™ 500 mcg powder for solution for injection should be reconstituted with 1.2 ml of sterile water for injection.

Nplate™ 250 mcg powder for solution for injection should be reconstituted with 0.72 ml of sterile water for injection.

Do not use saline or bacteriostatic water when reconstituting the product. Nplate™ should be reconstituted under aseptic conditions. The water for injection should be injected slowly into the Nplate™ vial. The vial contents may be swirled gently and inverted during dissolution. Do not shake or vigorously agitate the vial. Generally, dissolution of Nplate™ takes less than 2 minutes. Visually inspect the solution for particulate matter and discolouration before administration. Reconstituted Nplate™ should be clear and colourless. Nplate™ should not be administered if particulate matter and/or discolouration are observed.

The reconstituted product should be administered within 24 hours as it does not contain a preservative. The reconstituted product can remain at room temperature (25°C) or can be refrigerated at 2°C to 8°C for up to 24 hours prior to administration. The reconstituted product must be protected from light.

Any unused product or waste material should be disposed of in accordance with local requirements.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Nplate™ can cause side effects, although not everybody gets them.

Very common side effects (seen in more than 1 in 10 people taking Nplate™):

- joint pain (arthralgia);
- muscle pain or weakness (myalgia).
- pain in your hands and feet (extremities);
- headache;
- dizziness;
- abdominal pain;
- trouble sleeping (insomnia).

Common side effects (seen in more than 1 in 100, but less than 1 in 10, people taking Nplate™):

- increased bone marrow fibres (reticulín)
- low blood platelet count (thrombocytopenia) after stopping Nplate™;
- very high blood platelet count (thrombocythemia);
- shoulder pain
- tingling or numbness of the hands or feet (paresthesia);
- indigestion (dyspepsia).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor		Call your doctor
		Only if severe	In all cases	
Common (seen in more than 1 in 100 people taking Nplate™)	Low blood platelet count (thrombocytopenia) after stopping Nplate™		√	When you stop treatment with Nplate™, your platelet count may drop to the level it was before you started treatment with Nplate™. The symptoms associated with your ITP condition that you had prior to treatment with Nplate™ may recur, including bleeding. You should contact your doctor immediately if you stop taking Nplate™ or if your symptoms recur.
	Increased bone marrow fibres (reticulín)		√	This finding can only be diagnosed by your doctor with special testing. Your doctor will determine whether to continue you on Nplate™ or consider alternative treatment options.
	Very high platelet count (thrombocytosis)		√	You may potentially experience symptoms indicative of a blood clot. Symptoms may include, but are not limited to, headache, tingling in hands or feet, swelling and possible redness in areas such as the calf. Contact your doctor immediately.

A patient registry has been established for Nplate™. All patients are encouraged to participate and advised that their participation may involve long-term follow-up. Information on this registry program is available by calling 1-888-675-2836 (1-888-NPLATE-6) or by fax 1-888-675-2838 (1-888-NPLATE-8).

These are not all the possible symptoms or side effects you may experience; if you are concerned about any effects you experience you should contact your doctor.

