PRODUCT MONOGRAPH

PrNplate®
(romiplostim)

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

Professed Standard

Thrombopoiesis-Stimulating Protein

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Table of Contents

PrNplate®
(romiplostim)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

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 μg) is reconstituted with 1.2 mL of Sterile Water for Injection, USP and NPLATE (250 μg) is reconstituted with 0.72 mL of Sterile Water for Injection, USP. Reconstitution yields a clear, colourless, 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, 11 of 630 (1.7%) adult patients were observed to have reticulin in the bone marrow. NPLATE has been discontinued in some patients because of bone marrow reticulin deposition. Across all clinical studies, 2 patients developed collagen in the bone marrow. One of these patients had a history of ITP and hemolytic anemia.

Eleven patients were noted to have bone marrow reticulin deposition. One of these 11 patients also developed leukopenia in addition to underlying thrombocytopenia/ITP. All 11 patients with bone marrow reticulin deposition had received NPLATE doses ≥ 5 μg/kg and 7 had received doses ≥ 10 μg/kg.

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 anti-platelet therapy, reversal of anticoagulation, or platelet support.

Among the 630 adult ITP patients treated with NPLATE in clinical studies, 170 discontinued NPLATE treatment. Fourteen out of these 170 (8.2%) patients developed thrombocytopenia of greater severity than was present prior to NPLATE therapy.

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. Thrombocytosis events were observed in clinical studies with NPLATE. In controlled clinical studies, the incidence of thrombotic/thromboembolic complications was 2.4% in both NPLATE and placebo (the major treatment-emergent types of thombotic/thromboembolic complications reported in clinical studies included deep vein thrombosis, pulmonary embolism, myocardial infarction and thrombophlebitis). 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*). Thrombotic/thromboembolic events have been observed in the post-market setting (see *Adverse Drug Reactions, Post-Market Adverse Drug Reactions*).

Caution should be used when administering NPLATE to patients with known risk factors for thromboembolism including but not limited to inherited (eg, Factor V Leiden) or acquired risk factors (eg, ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking.

Cases of thromboembolic events (TEEs), including portal vein thrombosis, have been reported in patients with chronic liver disease receiving NPLATE. NPLATE should be used with caution in these populations.

Of the 630 adult patients who received NPLATE in ITP clinical studies, the study duration adjusted thrombotic/thromboembolic rate in subjects with age 65 years and over was 10 per 100 subject-years compared with 5.3 per 100 subject-years in the < 65 years age group (see *Warnings and Precautions, Special Populations – Geriatrics).*

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 $\geq 50x10^9$/L or to a level sufficient to avoid clinically important bleeding after four weeks at the highest weekly dose of 10 μg/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. Cases of hematologic malignancy were reported in NPLATE clinical studies. 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 clinical studies of treatment with NPLATE in patients with MDS (myelodysplastic syndrome), there were reported cases of progression to acute myeloid leukaemia (AML). In addition, there were some cases of transient blast cell increases, which did not progress to AML. NPLATE is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

In the Long-term ITP Extension Study (Study S4), there were 36 patients who reported neoplastic adverse events and 15 patients who reported skin-related neoplastic adverse events. In the Open-Label Study (Study S3), there were 14 patients in the NPLATE arm vs 5 patients in the SOC arm who reported neoplastic adverse events and 6 patients vs 0 patients, respectively who reported skin-related neoplastic adverse events (nonsplenectomized patients ≥ 18 years were randomized in a 2:1 ratio to NPLATE or medical SOC).

Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.

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.

Medication Errors

Medication errors including overdose and underdose have been reported in patients receiving NPLATE. Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications. If the platelet counts are excessively increased, discontinue NPLATE and monitor platelet counts. Reinitiate treatment with NPLATE in accordance with dosing and administration recommendations. Underdose may result in lower than expected platelet counts and potential for bleeding. Platelet counts should be monitored in patients receiving NPLATE (see *Dosage and Administration* and *Overdosage*).

Special Populations

Pregnant Women:

The safety and efficacy of NPLATE in pregnant women has not been established.NPLATE should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

Studies in animals have shown reproductive toxicity, such as transplacental passage and increased fetal platelet counts in rats.

Women who become pregnant during NPLATE treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-866-512-6436 to enroll.

Nursing Women:

It is not known whether NPLATE is present in human milk. However, excretion is likely and a risk to the suckling child cannot be excluded. Many drugs are excreted into human milk. Caution should be exercised when NPLATE is administered to women who are breast-feeding. Because of the potential for serious adverse reactions in nursing infants from NPLATE, a decision should be made by the mother and her physician concerning the overall relative benefits and risks of NPLATE therapy to both the mother and the infant.

Women who are nursing during NPLATE treatment are encouraged to enroll in Amgen's Lactation Surveillance Program. Patients or their physicians should call 1-866-512-6436 to enroll.

Pediatrics:

The safety and effectiveness of NPLATE in pediatric patients (< 18 years) have not been established. In an exploratory phase 1/2 dose-finding study of 22 pediatric patients (17 patients treated with NPLATE and 5 patients treated with placebo), the safety profile observed was similar to that of the adult population during the 12-week treatment period. However, bleeding events occurred in 12 (70.6%) subjects in the NPLATE arm vs 2 (40.0%) subjects in the placebo arm. One patient in the NPLATE arm had 3 moderate (CTCAE grade 2) bleeding events (epistaxis, contusion, petechiae). Bleeding events in the remaining patients were mild (CTCAE grade 1). For the placebo arm, all bleeding events occurred when the platelet count was $< 30 \times 10^9$/L. For the NPLATE arm, the majority of the bleeding adverse events occurred in the first 6 weeks of the treatment period, and most events (14 of 17) correlated to a platelet count of

$< 30 \times 10^9$/L; no bleeding events occurred at a platelet count $\geq 50 \times 10^9$/L. These results should be interpreted cautiously due to the small sample size.

Geriatrics:

Of the 630 adult patients who received NPLATE in ITP clinical studies, 171 (27%) were age 65 years and over, and 78 (12%) were 75 years 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.

Hepatic Impairment:

There is a lack of studies conducted in patients with hepatic impairment. NPLATE should be used with caution in this population.

Renal impairment:

There is a lack of studies conducted in patients with 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 630 adult patients with chronic ITP, ages 18 to 93 years, of whom 60% were female. NPLATE was studied in two randomized, placebo-controlled, double-blind studies that were identical in design, with the exception that Study S1 (Table 1and Table 3) evaluated nonsplenectomized patients with ITP and Study S2 (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.

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 (S1 and S2)

Table 1 and Table 2 presents adverse drug reactions from the two Phase 3 placebo-controlled studies (Study S1 and Study S2; 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 S1) and splenectomized (Study S2) patients.

Table 1. Adverse Drug Reactions ≥ 1 % Identified in Study S1 (Nonsplenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 20) n (%)	NPLATE (N = 42) n (%)
Number of Subjects Reporting At Least One of the Following Adverse Drug Reactions	10 (50.0)	29 (69.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	7 (35.0)	18 (42.9)
Arthralgia	5 (25.0)	10 (23.8)
Pain in Extremity	2 (10.0)	8 (19.0)
Shoulder Pain	0 (0.0)	5 (11.9)
Myalgia	1 (5.0)	3 (7.1)
NERVOUS SYSTEM DISORDERS	6 (30.0)	17 (40.5)
Headache	6 (30.0)	11 (26.2)
Dizziness	0 (0.0)	7 (16.7)
Paraesthesia	0 (0.0)	2 (4.8)
GASTROINTESTINAL DISORDERS	0 (0.0)	7 (16.7)
Abdominal Pain	0 (0.0)	5 (11.9)
Dyspepsia	0 (0.0)	2 (4.8)
PSYCHIATRIC DISORDERS	2 (10.0)	5 (11.9)
Insomnia	2 (10.0)	5 (11.9)

*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 ≥ 1% Identified in Study S2 (Splenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 21) n (%)	NPLATE (N = 42) n (%)
Number of Subjects Reporting At Least One of the Following Adverse Drug Reactions	9 (42.9)	32 (76.2)
NERVOUS SYSTEM DISORDERS	7 (33.3)	21 (50.0)
Headache	7 (33.3)	18 (42.9)
Dizziness	0 (0.0)	7 (16.7)
Paraesthesia	0 (0.0)	3 (7.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (14.3)	17 (40.5)
Arthralgia	3 (14.3)	12 (28.6)
Myalgia	0 (0.0)	9 (21.4)
Pain in Extremity	0 (0.0)	3 (7.1)
Shoulder Pain	0 (0.0)	2 (4.8)
PSYCHIATRIC DISORDERS	1 (4.8)	8 (19.0)
Insomnia	1 (4.8)	8 (19.0)
GASTROINTESTINAL DISORDERS	0 (0.0)	7 (16.7)
Abdominal Pain	0 (0.0)	4 (9.5)
Dyspepsia	0 (0.0)	4 (9.5)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	1 (2.4)
Bone Marrow Disorder[a]	0 (0.0)	1 (2.4)

[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 ≥ 2% difference (NPLATE vs. Placebo) in Study S1 (Nonsplenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 20) n (%)	NPLATE (N = 42) n (%)
Number of Subjects Reporting At Least One of the Following Adverse Events	7 (35.0)	40 (95.2)
GASTROINTESTINAL DISORDERS	2 (10.0)	19 (45.2)
Nausea	2 (10.0)	6 (14.3)
Gingival Bleeding	1 (5.0)	5 (11.9)
Abdominal Pain	0 (0.0)	5 (11.9)
Dyspepsia	0 (0.0)	2 (4.8)
Flatulence	0 (0.0)	2 (4.8)
Anal Fissure	0 (0.0)	1 (2.4)
Constipation	0 (0.0)	1 (2.4)
Gastritis	0 (0.0)	1 (2.4)
Gastrointestinal Haemorrhage	0 (0.0)	1 (2.4)
Haematochezia	0 (0.0)	1 (2.4)
Hiatus Hernia	0 (0.0)	1 (2.4)
Lip Haemorrhage	0 (0.0)	1 (2.4)
Umbilical Hernia	0 (0.0)	1 (2.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	3 (15.0)	18 (42.9)
Pain in Extremity	2 (10.0)	8 (19.0)
Back Pain	1 (5.0)	6 (14.3)
Shoulder Pain	0 (0.0)	5 (11.9)
Myalgia	1 (5.0)	3 (7.1)
Arthritis	0 (0.0)	1 (2.4)
Bone Pain	0 (0.0)	1 (2.4)
Coccydynia	0 (0.0)	1 (2.4)
Joint Stiffness	0 (0.0)	1 (2.4)
Muscular Weakness	0 (0.0)	1 (2.4)
Musculoskeletal Chest Pain	0 (0.0)	1 (2.4)
Musculoskeletal Pain	0 (0.0)	1 (2.4)
Musculoskeletal Stiffness	0 (0.0)	1 (2.4)
Tendonitis	0 (0.0)	1 (2.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (15.0)	14 (33.3)
Epistaxis	3 (15.0)	11 (26.2)
Allergic Sinusitis	0 (0.0)	1 (2.4)
Dysphonia	0 (0.0)	1 (2.4)
Dyspnoea Exertional	0 (0.0)	1 (2.4)
Haemoptysis	0 (0.0)	1 (2.4)
Pleural Effusion	0 (0.0)	1 (2.4)
INFECTIONS AND INFESTATIONS	2 (10.0)	13 (31.0)
Upper Respiratory Tract Infection	2 (10.0)	6 (14.3)
Herpes Simplex	0 (0.0)	2 (4.8)
Conjunctivitis Infective	0 (0.0)	1 (2.4)
Dental Caries	0 (0.0)	1 (2.4)
Ear Infection	0 (0.0)	1 (2.4)
Gastroenteritis Viral	0 (0.0)	1 (2.4)
Genital Infection Fungal	0 (0.0)	1 (2.4)
Oral Infection	0 (0.0)	1 (2.4)
Viral Infection	0 (0.0)	1 (2.4)

Table 3. Adverse Events with ≥ 2% difference (NPLATE vs. Placebo) in Study S1 (Nonsplenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 20) n (%)	NPLATE (N = 42) n (%)
NERVOUS SYSTEM DISORDERS	0 (0.0)	13 (31.0)
Dizziness	0 (0.0)	7 (16.7)
Dysarthria	0 (0.0)	2 (4.8)
Paraesthesia	0 (0.0)	2 (4.8)
Burning Sensation	0 (0.0)	1 (2.4)
Cerebrovascular Accident	0 (0.0)	1 (2.4)
Haemorrhage Intracranial	0 (0.0)	1 (2.4)
Lethargy	0 (0.0)	1 (2.4)
Sciatica	0 (0.0)	1 (2.4)
Sinus Headache	0 (0.0)	1 (2.4)
Tremor	0 (0.0)	1 (2.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (5.0)	9 (21.4)
Injection Site Bruising	1 (5.0)	5 (11.9)
Chest Pain	0 (0.0)	1 (2.4)
Influenza Like Illness	0 (0.0)	1 (2.4)
Injection Site Discomfort	0 (0.0)	1 (2.4)
Injection Site Pain	0 (0.0)	1 (2.4)
Non-Cardiac Chest Pain	0 (0.0)	1 (2.4)
Oedema Peripheral	0 (0.0)	1 (2.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0.0)	7 (16.7)
Excoriation	0 (0.0)	3 (7.1)
Head Injury	0 (0.0)	1 (2.4)
Muscle Strain	0 (0.0)	1 (2.4)
Road Traffic Accident	0 (0.0)	1 (2.4)
Scratch	0 (0.0)	1 (2.4)
Sternal Fracture	0 (0.0)	1 (2.4)
Thermal Burn	0 (0.0)	1 (2.4)
Wound	0 (0.0)	1 (2.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0.0)	7 (16.7)
Pruritus	0 (0.0)	3 (7.1)
Erythema	0 (0.0)	1 (2.4)
Hypotrichosis	0 (0.0)	1 (2.4)
Skin Discolouration	0 (0.0)	1 (2.4)
Skin Warm	0 (0.0)	1 (2.4)
RENAL AND URINARY DISORDERS	0 (0.0)	6 (14.3)
Hydronephrosis	0 (0.0)	2 (4.8)
Bladder Pain	0 (0.0)	1 (2.4)
Pollakiuria	0 (0.0)	1 (2.4)
Renal Artery Stenosis	0 (0.0)	1 (2.4)
Urinary Hesitation	0 (0.0)	1 (2.4)
Urine Abnormality	0 (0.0)	1 (2.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	5 (11.9)
Anaemia	0 (0.0)	3 (7.1)
Splenomegaly	0 (0.0)	2 (4.8)

Table 3. Adverse Events with ≥ 2% difference (NPLATE vs. Placebo) in Study S1 (Nonsplenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 20) n (%)	NPLATE (N = 42) n (%)
EYE DISORDERS	0 (0.0)	3 (7.1)
Eye Pruritus	0 (0.0)	1 (2.4)
Keratoconjunctivitis Sicca	0 (0.0)	1 (2.4)
Vision Blurred	0 (0.0)	1 (2.4)
PSYCHIATRIC DISORDERS	0 (0.0)	3 (7.1)
Depression	0 (0.0)	2 (4.8)
Confusional State	0 (0.0)	1 (2.4)
Suicidal Ideation	0 (0.0)	1 (2.4)
VASCULAR DISORDERS	0 (0.0)	3 (7.1)
Hot Flush	0 (0.0)	1 (2.4)
Hypertension	0 (0.0)	1 (2.4)
Hypertensive Crisis	0 (0.0)	1 (2.4)
INVESTIGATIONS	0 (0.0)	2 (4.8)
Blood Pressure Increased	0 (0.0)	1 (2.4)
Carotid Bruit	0 (0.0)	1 (2.4)
Weight Increased	0 (0.0)	1 (2.4)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	2 (4.8)
Diabetes Mellitus	0 (0.0)	1 (2.4)
Increased Appetite	0 (0.0)	1 (2.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0.0)	2 (4.8)
B-Cell Lymphoma	0 (0.0)	1 (2.4)
Basal Cell Carcinoma	0 (0.0)	1 (2.4)
CARDIAC DISORDERS	0 (0.0)	1 (2.4)
Pericardial Effusion	0 (0.0)	1 (2.4)
EAR AND LABYRINTH DISORDERS	0 (0.0)	1 (2.4)
Ear Congestion	0 (0.0)	1 (2.4)
ENDOCRINE DISORDERS	0 (0.0)	1 (2.4)
Hypothyroidism	0 (0.0)	1 (2.4)
HEPATOBILIARY DISORDERS	0 (0.0)	1 (2.4)
Hepatic Steatosis	0 (0.0)	1 (2.4)
IMMUNE SYSTEM DISORDERS	0 (0.0)	1 (2.4)
Hypersensitivity	0 (0.0)	1 (2.4)

Table 4. Adverse Events with ≥ 2% difference (NPLATE vs. Placebo) in Study S2 (Splenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 21) n (%)	NPLATE (N = 42) n (%)
Number of Subjects Reporting At Least One of the Following Adverse Events	18 (85.7)	42 (100.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (38.1)	27 (64.3)
Fatigue	5 (23.8)	13 (31.0)
Pain	2 (9.5)	6 (14.3)
Pyrexia	0 (0.0)	6 (14.3)
Oedema Peripheral	2 (9.5)	5 (11.9)
Asthenia	1 (4.8)	5 (11.9)
Injection Site Pain	1 (4.8)	4 (9.5)
Injection Site Bruising	1 (4.8)	3 (7.1)
Chills	0 (0.0)	3 (7.1)
Oedema	0 (0.0)	2 (4.8)
Face Oedema	0 (0.0)	1 (2.4)
Influenza Like Illness	0 (0.0)	1 (2.4)
Injection Site Swelling	0 (0.0)	1 (2.4)
NERVOUS SYSTEM DISORDERS	7 (33.3)	25 (59.5)
Headache	7 (33.3)	18 (42.9)
Dizziness	0 (0.0)	7 (16.7)
Paraesthesia	0 (0.0)	3 (7.1)
Migraine	0 (0.0)	2 (4.8)
Disturbance in Attention	0 (0.0)	1 (2.4)
Dysgeusia	0 (0.0)	1 (2.4)
Hypoaesthesia	0 (0.0)	1 (2.4)
Petit Mal Epilepsy	0 (0.0)	1 (2.4)
Psychomotor Hyperactivity	0 (0.0)	1 (2.4)
Syncope	0 (0.0)	1 (2.4)
Tension Headache	0 (0.0)	1 (2.4)
Visual Field Defect	0 (0.0)	1 (2.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	5 (23.8)	25 (59.5)
Arthralgia	3 (14.3)	12 (28.6)
Myalgia	0 (0.0)	9 (21.4)
Muscle Spasms	2 (9.5)	5 (11.9)
Musculoskeletal Chest Pain	0 (0.0)	3 (7.1)
Pain in Extremity	0 (0.0)	3 (7.1)
Bone Pain	0 (0.0)	2 (4.8)
Muscular Weakness	0 (0.0)	2 (4.8)
Shoulder Pain	0 (0.0)	2 (4.8)
Intervertebral Disc Protrusion	0 (0.0)	1 (2.4)
Musculoskeletal Stiffness	0 (0.0)	1 (2.4)
Tendonitis	0 (0.0)	1 (2.4)
GASTROINTESTINAL DISORDERS	5 (23.8)	24 (57.1)
Diarrhoea	2 (9.5)	9 (21.4)
Nausea	2 (9.5)	5 (11.9)
Oral Mucosal Blistering	2 (9.5)	5 (11.9)
Vomiting	1 (4.8)	4 (9.5)
Abdominal Pain	0 (0.0)	4 (9.5)
Dyspepsia	0 (0.0)	4 (9.5)

Table 4. Adverse Events with ≥ 2% difference (NPLATE vs. Placebo) in Study S2 (Splenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 21) n (%)	NPLATE (N = 42) n (%)
Abdominal Pain Upper	0 (0.0)	2 (4.8)
Haematochezia	0 (0.0)	2 (4.8)
Aphthous Stomatitis	0 (0.0)	1 (2.4)
Breath Odour	0 (0.0)	1 (2.4)
Constipation	0 (0.0)	1 (2.4)
Lip Blister	0 (0.0)	1 (2.4)
Mouth Haemorrhage	0 (0.0)	1 (2.4)
Rectal Haemorrhage	0 (0.0)	1 (2.4)
Stomach Discomfort	0 (0.0)	1 (2.4)
Tooth Discolouration	0 (0.0)	1 (2.4)
INFECTIONS AND INFESTATIONS	4 (19.0)	22 (52.4)
Upper Respiratory Tract Infection	3 (14.3)	8 (19.0)
Influenza	1 (4.8)	3 (7.1)
Viral Upper Respiratory Tract Infection	0 (0.0)	3 (7.1)
Bronchitis	0 (0.0)	2 (4.8)
Candidiasis	0 (0.0)	2 (4.8)
Acarodermatitis	0 (0.0)	1 (2.4)
Appendicitis	0 (0.0)	1 (2.4)
Body Tinea	0 (0.0)	1 (2.4)
Cellulitis	0 (0.0)	1 (2.4)
Fungal Infection	0 (0.0)	1 (2.4)
Gastroenteritis	0 (0.0)	1 (2.4)
Gastrointestinal Infection	0 (0.0)	1 (2.4)
Herpes Simplex	0 (0.0)	1 (2.4)
Oral Candidiasis	0 (0.0)	1 (2.4)
Pharyngitis	0 (0.0)	1 (2.4)
Skin Infection	0 (0.0)	1 (2.4)
Tooth Infection	0 (0.0)	1 (2.4)
Viral Infection	0 (0.0)	1 (2.4)
Vulvovaginal Mycotic Infection	0 (0.0)	1 (2.4)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	8 (38.1)	21 (50.0)
Epistaxis	7 (33.3)	16 (38.1)
Cough	3 (14.3)	7 (16.7)
Pharyngolaryngeal Pain	0 (0.0)	6 (14.3)
Rhinitis Allergic	0 (0.0)	3 (7.1)
Haemoptysis	0 (0.0)	2 (4.8)
Nasal Congestion	0 (0.0)	2 (4.8)
Sleep Apnoea Syndrome	0 (0.0)	2 (4.8)
Allergic Sinusitis	0 (0.0)	1 (2.4)
Dry Throat	0 (0.0)	1 (2.4)
Dysphonia	0 (0.0)	1 (2.4)
Paranasal Sinus Hypersecretion	0 (0.0)	1 (2.4)
Pleural Effusion	0 (0.0)	1 (2.4)
Sputum Discoloured	0 (0.0)	1 (2.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (4.8)	13 (31.0)
Alopecia	1 (4.8)	3 (7.1)
Acne	0 (0.0)	2 (4.8)

Table 4. Adverse Events with ≥ 2% difference (NPLATE vs. Placebo) in Study S2 (Splenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 21) n (%)	NPLATE (N = 42) n (%)
Skin Haemorrhage	0 (0.0)	2 (4.8)
Angioneurotic Oedema	0 (0.0)	1 (2.4)
Dermal Cyst	0 (0.0)	1 (2.4)
Dry Skin	0 (0.0)	1 (2.4)
Hair Growth Abnormal	0 (0.0)	1 (2.4)
Nail Disorder	0 (0.0)	1 (2.4)
Photosensitivity Reaction	0 (0.0)	1 (2.4)
Prurigo	0 (0.0)	1 (2.4)
Rash Papular	0 (0.0)	1 (2.4)
Skin Lesion	0 (0.0)	1 (2.4)
Skin Odour Abnormal	0 (0.0)	1 (2.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (14.3)	12 (28.6)
Contusion	3 (14.3)	8 (19.0)
Excoriation	0 (0.0)	1 (2.4)
Fall	0 (0.0)	1 (2.4)
Soft Tissue Injury	0 (0.0)	1 (2.4)
Tongue Injury	0 (0.0)	1 (2.4)
Wound	0 (0.0)	1 (2.4)
PSYCHIATRIC DISORDERS	1 (4.8)	9 (21.4)
Insomnia	1 (4.8)	8 (19.0)
Nightmare	0 (0.0)	1 (2.4)
Suicide Attempt	0 (0.0)	1 (2.4)
VASCULAR DISORDERS	0 (0.0)	8 (19.0)
Haematoma	0 (0.0)	4 (9.5)
Flushing	0 (0.0)	2 (4.8)
Hot Flush	0 (0.0)	2 (4.8)
Peripheral Embolism	0 (0.0)	1 (2.4)
Peripheral Ischaemia	0 (0.0)	1 (2.4)
INVESTIGATIONS	0 (0.0)	7 (16.7)
Weight Increased	0 (0.0)	3 (7.1)
Blood Pressure Increased	0 (0.0)	2 (4.8)
Alanine Aminotransferase Increased	0 (0.0)	1 (2.4)
Aspartate Aminotransferase Increased	0 (0.0)	1 (2.4)
Heart Rate Increased	0 (0.0)	1 (2.4)
Hepatitis C Antibody Positive	0 (0.0)	1 (2.4)
Weight Decreased	0 (0.0)	1 (2.4)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0.0)	7 (16.7)
Menorrhagia	0 (0.0)	2 (4.8)
Metrorrhagia	0 (0.0)	2 (4.8)
Dysmenorrhoea	0 (0.0)	1 (2.4)
Gynaecomastia	0 (0.0)	1 (2.4)
Postmenopausal Haemorrhage	0 (0.0)	1 (2.4)
Uterine Polyp	0 (0.0)	1 (2.4)
Vaginal Haemorrhage	0 (0.0)	1 (2.4)

Table 4. Adverse Events with ≥ 2% difference (NPLATE vs. Placebo) in Study S2 (Splenectomized Patients)

SYSTEM ORGAN CLASS Preferred Term	Placebo (N = 21) n (%)	NPLATE (N = 42) n (%)
EYE DISORDERS	0 (0.0)	5 (11.9)
Lacrimation Increased	0 (0.0)	2 (4.8)
Ocular Hyperaemia	0 (0.0)	1 (2.4)
Scleral Haemorrhage	0 (0.0)	1 (2.4)
Visual Disturbance	0 (0.0)	1 (2.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0 (0.0)	4 (9.5)
Thrombocytopenia	0 (0.0)	2 (4.8)
Bone Marrow Disorder	0 (0.0)	1 (2.4)
Idiopathic Thrombocytopenic Purpura	0 (0.0)	1 (2.4)
METABOLISM AND NUTRITION DISORDERS	0 (0.0)	4 (9.5)
Dehydration	0 (0.0)	1 (2.4)
Hypokalaemia	0 (0.0)	1 (2.4)
Hypovolaemia	0 (0.0)	1 (2.4)
Vitamin B12 Deficiency	0 (0.0)	1 (2.4)
CARDIAC DISORDERS	0 (0.0)	3 (7.1)
Angina Pectoris	0 (0.0)	2 (4.8)
Cardiac Failure Congestive	0 (0.0)	1 (2.4)
Extrasystoles	0 (0.0)	1 (2.4)
EAR AND LABYRINTH DISORDERS	0 (0.0)	2 (4.8)
Ear Haemorrhage	0 (0.0)	1 (2.4)
Tinnitus	0 (0.0)	1 (2.4)
IMMUNE SYSTEM DISORDERS	0 (0.0)	2 (4.8)
Hypersensitivity	0 (0.0)	1 (2.4)
Seasonal Allergy	0 (0.0)	1 (2.4)
ENDOCRINE DISORDERS	0 (0.0)	1 (2.4)
Goitre	0 (0.0)	1 (2.4)
HEPATOBILIARY DISORDERS	0 (0.0)	1 (2.4)
Cholelithiasis	0 (0.0)	1 (2.4)

Long-term ITP Extension Study (Study S4)

An analysis was done for subjects from 8 ITP studies who completed their parent study and entered the ongoing open label extension study 20030213. A total of 292 adult subjects were enrolled, and 291 adult subjects received at least 1 dose of NPLATE. The median time on study for the 291 adult subjects in the safety analysis set was 78 weeks (SD, 72.7 weeks; range, 1 to 277 weeks).

Adverse events with a subject incidence ≥ 10% were headache (37.5%), nasopharyngitis (34.4%), fatigue (32.0%), contusion (30.6%), upper respiratory tract infection (26.1%), diarrhea (25.1%), epistaxis (25.1%), cough (24.1%), nausea (24.1%), arthralgia (23.7%), pain in extremity (19.2%), petechiae (18.9%), back pain (18.6%), dizziness (17.5%), oropharyngeal pain (17.2%), rash (15.8%), vomiting (15.8%), gingival bleeding (15.5%), insomnia (14.1%), edema peripheral (14.1%), hematoma (13.1%), pyrexia (13.1%), sinusitis (13.1%), urinary tract

infection (12.4%), myalgia (12.0%), abdominal pain (11.7%), idiopathic thrombocytopenic purpura (11.7%), thrombocytopenia (11.3%), pain (11.0%), and nasal congestion (10.3%). Serious adverse events were reported for 117 adult subjects (40.2%). Adverse events leading to study withdrawal were reported for 23 (7.9%) adult subjects.

Eighteen serious thrombotic or thromboembolic events were reported in 14/291 (4.8%) subjects. Thrombotic or thromboembolic events were reported in 19 (6.5%) adult subjects. Reports that mentioned fibrosis or reticulin in the bone marrow were received for 9 subjects. In addition, bone marrow reticulin was noted in reports of adverse events in 5 other subjects. Renal impairment adverse events were reported in 10 (3.4%) adult subjects. Sixteen adult subjects died during this study. Two events of death were considered treatment related, one event each of myocardial infarction and angina unstable. Pre-existing risk factors for these fatal events were present for each of these subjects. Eight of the 16 deaths were due to cardiac events. Forty (13.7%) subjects experienced cardiac adverse events**.** However, there is insufficient evidence to support a causal association between NPLATE therapy and the risk of cardiac disorders and worsening of pre-existing disorders.

Table 5, Table 6, Table 7, and Table 8 presents Adverse Drug Reactions with a subject incidence ≥ 1%; Adverse Events with a subject incidence ≥ 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 ≥ 1 % in Study S4
(Adult Population)

SYSTEM ORGAN CLASS **Preferred Term**	**NPLATE (N = 291) n (%)**
Number of Subjects Reporting At Least One of the Following Adverse Drug Reactions	195 (67.0)
NERVOUS SYSTEM DISORDERS	134 (46.0)
Headache	109 (37.5)
Dizziness	51 (17.5)
Paraesthesia	28 (9.6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	116 (39.9)
Arthralgia	69 (23.7)
Pain in extremity	56 (19.2)
Myalgia	35 (12.0)
GASTROINTESTINAL DISORDERS	49 (16.8)
Abdominal pain	34 (11.7)
Dyspepsia	20 (6.9)
PSYCHIATRIC DISORDERS	41 (14.1)
Insomnia	41 (14.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	5 (1.7)
Bone marrow disorder	5 (1.7)

Table 6. Subject Incidence of Adverse Events with Subject Incidence ≥ 2 % in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Number of Subjects Reporting At Least One of the Following Adverse Event	278 (95.5)
INFECTIONS AND INFESTATIONS	202 (69.4)
Nasopharyngitis	100 (34.4)
Upper respiratory tract infection	76 (26.1)
Sinusitis	38 (13.1)
Urinary tract infection	36 (12.4)
Bronchitis	24 (8.2)
Influenza	23 (7.9)
Gastroenteritis	14 (4.8)
Pharyngitis	14 (4.8)
Pneumonia	12 (4.1)
Ear infection	11 (3.8)
Respiratory tract infection	11 (3.8)
Rhinitis	11 (3.8)
Cellulitis	10 (3.4)
Herpes zoster	9 (3.1)
Tooth abscess	9 (3.1)
Tooth infection	8 (2.7)
Viral upper respiratory tract infection	7 (2.4)
Cystitis	6 (2.1)
Eye infection	6 (2.1)
Helicobacter infection	6 (2.1)
Laryngitis	6 (2.1)
Oral herpes	6 (2.1)
GASTROINTESTINAL DISORDERS	170 (58.4)
Diarrhoea	73 (25.1)
Nausea	70 (24.1)
Vomiting	46 (15.8)
Gingival bleeding	45 (15.5)
Abdominal pain	34 (11.7)
Constipation	26 (8.9)
Abdominal pain upper	22 (7.6)
Mouth haemorrhage	22 (7.6)
Dyspepsia	20 (6.9)
Abdominal discomfort	17 (5.8)
Toothache	17 (5.8)
Rectal haemorrhage	12 (4.1)
Abdominal distension	9 (3.1)
Stomatitis	9 (3.1)

Table 6. Subject Incidence of Adverse Events with Subject Incidence ≥ 2 % in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Haemorrhoids	7 (2.4)
Abdominal pain lower	6 (2.1)
Gastrointestinal haemorrhage	6 (2.1)
Gastrooesophageal reflux disease	6 (2.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	163 (56.0)
Arthralgia	69 (23.7)
Pain in extremity	56 (19.2)
Back pain	54 (18.6)
Myalgia	35 (12.0)
Musculoskeletal pain	29 (10.0)
Muscle spasms	28 (9.6)
Joint swelling	16 (5.5)
Arthritis	13 (4.5)
Musculoskeletal chest pain	10 (3.4)
Osteoarthritis	10 (3.4)
Bone pain	9 (3.1)
Musculoskeletal stiffness	8 (2.7)
Neck pain	7 (2.4)
Flank pain	6 (2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	160 (55.0)
Epistaxis	73 (25.1)
Cough	70 (24.1)
Oropharyngeal pain	50 (17.2)
Nasal congestion	30 (10.3)
Rhinorrhoea	26 (8.9)
Dyspnoea	24 (8.2)
Oropharyngeal blistering	20 (6.9)
Dyspnoea exertional	11 (3.8)
Respiratory tract congestion	9 (3.1)
Sinus congestion	9 (3.1)
Asthma	7 (2.4)
Dysphonia	7 (2.4)
Respiratory disorder	6 (2.1)
Throat irritation	6 (2.1)
NERVOUS SYSTEM DISORDERS	154 (52.9)
Headache	109 (37.5)
Dizziness	51 (17.5)
Paraesthesia	28 (9.6)
Migraine	16 (5.5)

Table 6. Subject Incidence of Adverse Events with Subject Incidence ≥ 2 % in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Hypoaesthesia	12 (4.1)
Sinus headache	10 (3.4)
Sciatica	9 (3.1)
Tremor	9 (3.1)
Lethargy	7 (2.4)
Neuropathy peripheral	7 (2.4)
Somnolence	6 (2.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	153 (52.6)
Fatigue	93 (32.0)
Oedema peripheral	41 (14.1)
Pyrexia	38 (13.1)
Pain	32 (11.0)
Asthenia	23 (7.9)
Chest pain	17 (5.8)
Injection site haematoma	15 (5.2)
Chills	12 (4.1)
Injection site pain	12 (4.1)
Chest discomfort	9 (3.1)
Influenza like illness	9 (3.1)
Mucosal haemorrhage	7 (2.4)
Malaise	6 (2.1)
Oedema	6 (2.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	148 (50.9)
Petechiae	55 (18.9)
Rash	46 (15.8)
Ecchymosis	26 (8.9)
Pruritus	23 (7.9)
Blood blister	19 (6.5)
Skin lesion	18 (6.2)
Urticaria	13 (4.5)
Erythema	12 (4.1)
Purpura	12 (4.1)
Eczema	11 (3.8)
Dermatitis	7 (2.4)
Psoriasis	7 (2.4)
Acne	6 (2.1)
Alopecia	6 (2.1)
Hyperhidrosis	6 (2.1)
Swelling face	6 (2.1)

Table 6. Subject Incidence of Adverse Events with Subject Incidence ≥ 2 % in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	125 (43.0)
Contusion	89 (30.6)
Fall	19 (6.5)
Skin laceration	18 (6.2)
Procedural pain	17 (5.8)
Joint sprain	11 (3.8)
Excoriation	10 (3.4)
Eye injury	7 (2.4)
Wound	7 (2.4)
Arthropod bite	6 (2.1)
Thermal burn	6 (2.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	67 (23.0)
Idiopathic thrombocytopenic purpura	34 (11.7)
Thrombocytopenia	33 (11.3)
Anaemia	19 (6.5)
VASCULAR DISORDERS	65 (22.3)
Haematoma	38 (13.1)
Hypertension	17 (5.8)
Haemorrhage	11 (3.8)
Hot flush	7 (2.4)
PSYCHIATRIC DISORDERS	64 (22.0)
Insomnia	41 (14.1)
Anxiety	22 (7.6)
Depression	19 (6.5)
EYE DISORDERS	41 (14.1)
Conjunctival haemorrhage	8 (2.7)
Conjunctivitis	8 (2.7)
Ocular hyperaemia	8 (2.7)
Vision blurred	8 (2.7)
Visual impairment	7 (2.4)
Dry eye	6 (2.1)
Eye pain	6 (2.1)
METABOLISM AND NUTRITION DISORDERS	35 (12.0)
Decreased appetite	15 (5.2)
Dehydration	9 (3.1)
Hypokalaemia	9 (3.1)
Hyperglycaemia	6 (2.1)

Table 6. Subject Incidence of Adverse Events with Subject Incidence ≥ 2 % in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	28 (9.6)
Menorrhagia	14 (4.8)
Vaginal haemorrhage	14 (4.8)
IMMUNE SYSTEM DISORDERS	27 (9.3)
Seasonal allergy	16 (5.5)
Hypersensitivity	12 (4.1)
EAR AND LABYRINTH DISORDERS	26 (8.9)
Ear pain	13 (4.5)
Tinnitus	9 (3.1)
Vertigo	9 (3.1)
CARDIAC DISORDERS	20 (6.9)
Cardiac failure congestive	7 (2.4)
Palpitations	7 (2.4)
Tachycardia	7 (2.4)
INVESTIGATIONS	20 (6.9)
Platelet count decreased	8 (2.7)
Weight decreased	6 (2.1)
Weight increased	6 (2.1)
RENAL AND URINARY DISORDERS	20 (6.9)
Dysuria	15 (5.2)
Pollakiuria	8 (2.7)
SURGICAL AND MEDICAL PROCEDURES	11 (3.8)
Tooth extraction	11 (3.8)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	6 (2.1)
Basal cell carcinoma	6 (2.1)

Table 7. Subject Incidence of Serious Adverse Events in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Number of Subjects Reporting At Least One of the Following Serious Adverse Events	117 (40.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	33 (11.3)
Thrombocytopenia	23 (7.9)
Idiopathic thrombocytopenic purpura	7 (2.4)
Bone marrow disorder	4 (1.4)
Anaemia	3 (1.0)
Bicytopenia	1 (0.3)
Bone marrow reticulin fibrosis	1 (0.3)
Evans syndrome	1 (0.3)
Haemolytic anaemia	1 (0.3)
Leukocytosis	1 (0.3)
Neutropenia	1 (0.3)
INFECTIONS AND INFESTATIONS	27 (9.3)
Pneumonia	8 (2.7)
Bronchitis	3 (1.0)
Cellulitis	3 (1.0)
Appendicitis	2 (0.7)
Catheter related infection	2 (0.7)
Urosepsis	2 (0.7)
Anal abscess	1 (0.3)
Bacteraemia	1 (0.3)
Candidiasis	1 (0.3)
Catheter bacteraemia	1 (0.3)
Device related infection	1 (0.3)
Epiglottitis	1 (0.3)
Gastroenteritis	1 (0.3)
Haematoma infection	1 (0.3)
Klebsiella sepsis	1 (0.3)
Localised infection	1 (0.3)
Meningitis listeria	1 (0.3)
Nasopharyngitis	1 (0.3)
Parotitis	1 (0.3)
Pneumococcal sepsis	1 (0.3)
Pneumonia streptococcal	1 (0.3)
Post procedural cellulitis	1 (0.3)
Progressive multifocal leukoencephalopathy	1 (0.3)
Sepsis	1 (0.3)
Thrombophlebitis septic	1 (0.3)
Tooth abscess	1 (0.3)

Table 7. Subject Incidence of Serious Adverse Events in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
GASTROINTESTINAL DISORDERS	25 (8.6)
Gastrointestinal haemorrhage	4 (1.4)
Abdominal pain	2 (0.7)
Colitis	2 (0.7)
Gingival bleeding	2 (0.7)
Rectal haemorrhage	2 (0.7)
Abdominal distension	1 (0.3)
Abdominal pain lower	1 (0.3)
Abdominal pain upper	1 (0.3)
Anal fistula	1 (0.3)
Ascites	1 (0.3)
Colitis ischaemic	1 (0.3)
Diarrhoea	1 (0.3)
Dyspepsia	1 (0.3)
Femoral hernia	1 (0.3)
Haematemesis	1 (0.3)
Irritable bowel syndrome	1 (0.3)
Mouth cyst	1 (0.3)
Mouth haemorrhage	1 (0.3)
Mouth ulceration	1 (0.3)
Nausea	1 (0.3)
Periodontitis	1 (0.3)
Small intestinal obstruction	1 (0.3)
Tooth impacted	1 (0.3)
Tooth loss	1 (0.3)
Upper gastrointestinal haemorrhage	1 (0.3)
Vomiting	1 (0.3)
CARDIAC DISORDERS	18 (6.2)
Cardiac failure congestive	5 (1.7)
Myocardial infarction	5 (1.7)
Cardiac failure	4 (1.4)
Acute myocardial infarction	3 (1.0)
Atrial fibrillation	3 (1.0)
Angina unstable	2 (0.7)
Coronary artery disease	2 (0.7)
Cardiac arrest	1 (0.3)
Cardiac tamponade	1 (0.3)
Pericardial haemorrhage	1 (0.3)
Trifascicular block	1 (0.3)

Table 7. Subject Incidence of Serious Adverse Events in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
NERVOUS SYSTEM DISORDERS	15 (5.2)
Cerebrovascular accident	2 (0.7)
Convulsion	2 (0.7)
Syncope	2 (0.7)
Transient ischaemic attack	2 (0.7)
Complex regional pain syndrome	1 (0.3)
Headache	1 (0.3)
Intracranial aneurysm	1 (0.3)
Loss of consciousness	1 (0.3)
Migraine	1 (0.3)
Multiple sclerosis relapse	1 (0.3)
Presyncope	1 (0.3)
Transverse sinus thrombosis	1 (0.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13 (4.5)
Pyrexia	4 (1.4)
Chest pain	3 (1.0)
Hernia obstructive	2 (0.7)
Adverse drug reaction	1 (0.3)
Asthenia	1 (0.3)
Death	1 (0.3)
Fatigue	1 (0.3)
Generalised oedema	1 (0.3)
Hernia	1 (0.3)
Hernia pain	1 (0.3)
Hyperpyrexia	1 (0.3)
Mechanical complication of implant	1 (0.3)
Oedema peripheral	1 (0.3)
HEPATOBILIARY DISORDERS	11 (3.8)
Cholelithiasis	3 (1.0)
Cholecystitis	2 (0.7)
Hepatic failure	2 (0.7)
Biliary colic	1 (0.3)
Cholecystitis acute	1 (0.3)
Hepatic steatosis	1 (0.3)
Hepatitis	1 (0.3)
Portal vein thrombosis	1 (0.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	11 (3.8)
Hip fracture	2 (0.7)
Arteriovenous fistula site complication	1 (0.3)

Table 7. Subject Incidence of Serious Adverse Events in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Contusion	1 (0.3)
Fractured sacrum	1 (0.3)
Head injury	1 (0.3)
Humerus fracture	1 (0.3)
Incisional hernia	1 (0.3)
Medical device complication	1 (0.3)
Meniscus lesion	1 (0.3)
Pelvic fracture	1 (0.3)
Subdural haemorrhage	1 (0.3)
Upper limb fracture	1 (0.3)
Wound	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	11 (3.8)
Hepatic neoplasm malignant	2 (0.7)
Breast cancer	1 (0.3)
Chronic lymphocytic leukaemia	1 (0.3)
Colon cancer recurrent	1 (0.3)
Lung neoplasm malignant	1 (0.3)
Lymphoma	1 (0.3)
Metastases to central nervous system	1 (0.3)
Multiple myeloma	1 (0.3)
Myelofibrosis	1 (0.3)
Neoplasm of orbit	1 (0.3)
Renal cell carcinoma	1 (0.3)
Transitional cell carcinoma	1 (0.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11 (3.8)
Dyspnoea	4 (1.4)
Epistaxis	3 (1.0)
Respiratory failure	2 (0.7)
Acute pulmonary oedema	1 (0.3)
Asthma	1 (0.3)
Cough	1 (0.3)
Haemoptysis	1 (0.3)
Pleuritic pain	1 (0.3)
Pulmonary embolism	1 (0.3)
Pulmonary haemorrhage	1 (0.3)
Respiratory arrest	1 (0.3)
VASCULAR DISORDERS	9 (3.1)
Deep vein thrombosis	2 (0.7)
Aortic aneurysm	1 (0.3)

Table 7. Subject Incidence of Serious Adverse Events in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Femoral arterial stenosis	1 (0.3)
Haematoma	1 (0.3)
Haemorrhage	1 (0.3)
Phlebitis	1 (0.3)
Subgaleal haematoma	1 (0.3)
Thrombosis	1 (0.3)
METABOLISM AND NUTRITION DISORDERS	8 (2.7)
Dehydration	4 (1.4)
Hyperkalaemia	2 (0.7)
Decreased appetite	1 (0.3)
Hypokalaemia	1 (0.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (2.7)
Osteoarthritis	3 (1.0)
Arthritis	1 (0.3)
Intervertebral disc protrusion	1 (0.3)
Osteonecrosis	1 (0.3)
Pain in extremity	1 (0.3)
Rhabdomyolysis	1 (0.3)
RENAL AND URINARY DISORDERS	7 (2.4)
Renal failure	3 (1.0)
Renal failure acute	2 (0.7)
Renal failure chronic	1 (0.3)
Urinary bladder polyp	1 (0.3)
Urinary retention	1 (0.3)
INVESTIGATIONS	6 (2.1)
Platelet count decreased	3 (1.0)
Platelet count increased	2 (0.7)
Megakaryocytes increased	1 (0.3)
PSYCHIATRIC DISORDERS	6 (2.1)
Anxiety	2 (0.7)
Mental status changes	2 (0.7)
Agitation	1 (0.3)
Confusional state	1 (0.3)
Suicidal ideation	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	6 (2.1)
Petechiae	2 (0.7)
Rash	2 (0.7)
Blister	1 (0.3)
Ecchymosis	1 (0.3)

Table 7. Subject Incidence of Serious Adverse Events in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Psoriasis	1 (0.3)
Purpura	1 (0.3)
Systemic lupus erythematosus rash	1 (0.3)
Urticaria	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5 (1.7)
Vaginal haemorrhage	2 (0.7)
Menorrhagia	1 (0.3)
Metrorrhagia	1 (0.3)
Ovarian cyst	1 (0.3)
SURGICAL AND MEDICAL PROCEDURES	5 (1.7)
Knee arthroplasty	2 (0.7)
Cholecystectomy	1 (0.3)
Elective surgery	1 (0.3)
Plastic surgery	1 (0.3)
Skin cosmetic procedure	1 (0.3)
Stent placement	1 (0.3)
EAR AND LABYRINTH DISORDERS	3 (1.0)
Vertigo	2 (0.7)
Vestibular disorder	1 (0.3)
EYE DISORDERS	2 (0.7)
Blindness	1 (0.3)
Conjunctival haemorrhage	1 (0.3)
Papilloedema	1 (0.3)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	1 (0.3)
Atrial septal defect	1 (0.3)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.3)
Abortion spontaneous	1 (0.3)

Table 8. Subject Incidence of Adverse Events Leading to Study Withdrawal in Study S4 (Adult Population)

SYSTEM ORGAN CLASS Preferred Term	NPLATE (N = 291) n (%)
Number of Subjects Reporting At Least One of the Following Adverse Events Leading to Study Withdrawal	23 (7.9)
CARDIAC DISORDERS	7 (2.4)
Myocardial infarction	3 (1.0)
Angina unstable	1 (0.3)
Cardiac arrest	1 (0.3)
Cardiac failure congestive	1 (0.3)
Cardiac tamponade	1 (0.3)
INFECTIONS AND INFESTATIONS	4 (1.4)
Meningitis listeria	1 (0.3)
Pneumococcal sepsis	1 (0.3)
Pneumonia streptococcal	1 (0.3)
Thrombophlebitis septic	1 (0.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (1.4)
Hepatic neoplasm malignant	1 (0.3)
Lymphoma	1 (0.3)
Multiple myeloma	1 (0.3)
Myelofibrosis	1 (0.3)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.7)
Bone marrow disorder	2 (0.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.3)
Death	1 (0.3)
INVESTIGATIONS	1 (0.3)
Platelet count decreased	1 (0.3)
RENAL AND URINARY DISORDERS	1 (0.3)
Renal failure	1 (0.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.3)
Vaginal haemorrhage	1 (0.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (0.3)
Systemic lupus erythematosus rash	1 (0.3)
VASCULAR DISORDERS	1 (0.3)
Deep vein thrombosis	1 (0.3)

Open-Label Study (Study S3)

During the overall treatment period, 156 subjects in the NPLATE arm and 73 subjects in the SOC arm were summarized.

In the NPLATE arm, adverse events with a subject incidence ≥ 10% were headache (34.6%), fatigue (27.6%), nasopharyngitis (23.1%), epistaxis (19.2%), petechiae (16.0%), nausea (16.0%), arthralgia (16.0%), cough (16.0%), contusion (14.7%), pain in extremity (14.1%), dizziness (13.5%), diarrhea (13.5%), urinary tract infection (12.2%), oropharyngeal pain (12.2%), upper respiratory tract infection (11.5%), back pain (11.5%), myalgia (10.9%), constipation (10.3%), pruritus (10.3%), and oedema peripheral (10.3%). In addition, the subject incidence was 12.8% for renal impairment, 5.1% for leukocytosis and anemia, and 3.8% for thrombotic/thromboembolic events.

In the SOC arm, adverse events with a subject incidence ≥ 10% were epistaxis (23.3%), fatigue (21.9%), headache (19.2%), nasopharyngitis (19.2%), contusion (17.8%), petechiae (17.8%), and urinary tract infection (11.0%). In addition, the subject incidence was 11.0% for renal impairment, 4.1% for thrombotic/thromboembolic events, and 1.4% for leukocytosis and anemia.

Serious adverse events were reported by 36 (23.1%) subjects in the NPLATE arm and 28 (38.4%) subjects in the SOC arm.

Adverse events leading to study withdrawal were reported by 6 (3.8%) subjects in the NPLATE arm and 3 (4.1%) subjects in the SOC arm.

Seven serious thrombotic/thromboembolic events were reported in 5 (3.2%) subjects in the NPLATE arm. No serious thrombotic/thromboembolic events were reported in the SOC arm. No subjects experienced bone marrow fibrosis/reticulin adverse events in the NPLATE arm or SOC arm. Six subjects died during this study: 1 subject in the NPLATE arm and 5 subjects in the SOC arm. None of the deaths were considered to be treatment related. Two of the 5 deaths in the SOC arm were attributed to cardiac events. Eleven (7.1%) subjects in the NPLATE arm experienced cardiac adverse events. Nine (12.3%) subjects in the SOC arm experienced cardiac adverse events. There is insufficient evidence to support a causal association between NPLATE and the risk of cardiac disorders and worsening of pre-existing disorders.

Bleeding Events

In two pivotal phase 3 adult ITP studies, an inverse relationship between bleeding events and platelet counts was observed. One hundred ninety-three of 630 (30.6%) adult subjects developed bleeding events that occurred at platelet counts < 20 x 10^9/L. Ninety-two of 630 (14.6%) adult subjects developed bleeding events ≥ grade 2 that occurred at platelet counts < 50 x 10^9/L.

In these 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 long-term extension study (S4), bleeding events were reported in 166 (57.0%) adult subjects. In the open-label study (S3), bleeding events were reported in 81 (51.9%) subjects in the NPLATE arm and 40 (54.8%) subjects in the SOC arm.

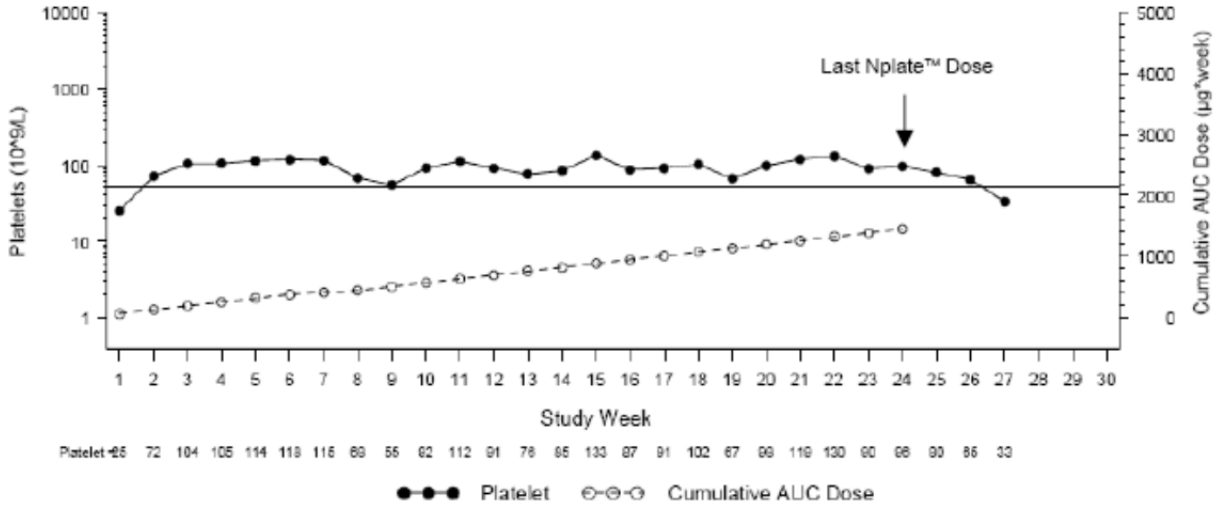
Bleeding events in Subjects with Variable Platelet Counts (Unstable Platelet Counts)

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.

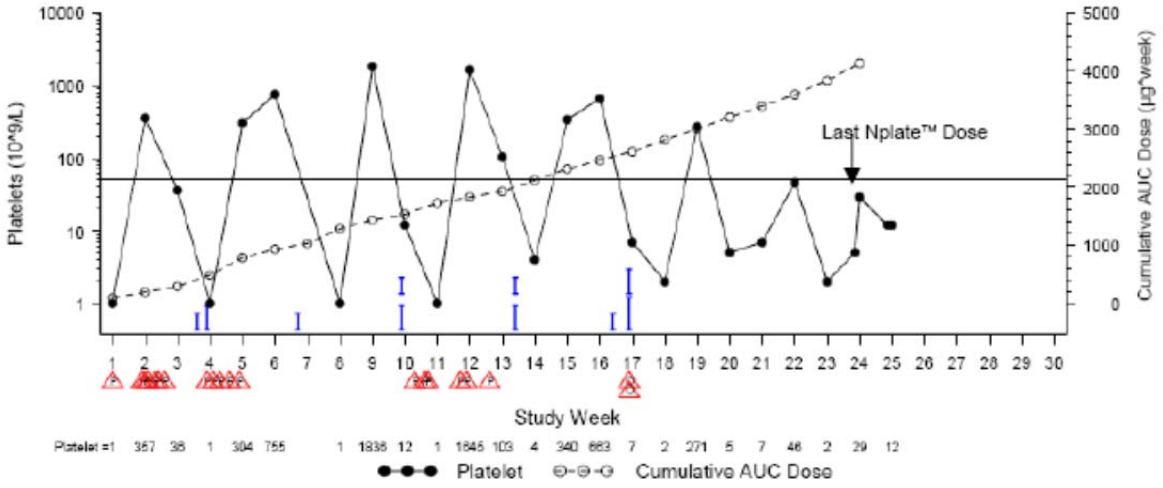
Figure 1 and Figure 2 provide a representation of two individual subjects treated with NPLATE who experienced stable and unstable platelet counts, respectively.

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 NPLATE using a Biacore-based biosensor immunoassay. This assay is capable of detecting both high and low affinity binding antibodies that bind to NPLATE 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.

Of the 510/630 adult ITP subjects dosed with NPLATE that were evaluated for immunogenicity, 20/510 (3.9%) subjects showed a pre-existing binding antibody response to NPLATE and 20/510 (3.9%) subjects had a pre-existing binding antibody response to TPO. The incidence of binding antibodies that developed against NPLATE and TPO was 8.4% (43/510) and 3.9% (20/510), respectively. The incidence of neutralizing antibodies that developed against NPLATE was 0.4% (2/510) and 0% for TPO, respectively. The incidence of pre-existing neutralizing antibody response to NPLATE was 0% and to TPO was 0.2% (1/510), respectively. 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 NPLATE 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.

Post-Market Adverse Drug Reactions

In addition to the events listed above, reports of an adverse reaction have been identified post-market in patients receiving NPLATE, including:

- Erythromelalgia
- Hypersensitivity
- Angioedema
- Thrombotic/thromboembolic events

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 μg/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 μg/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 μg/kg.

Adjust the dose as follows:

- If the platelet count is < 50 x 10^9/L, increase the dose by 1 μg/kg every 1-2 weeks.
- If platelet count is > 200 x 10^9/L for 2 consecutive weeks, reduce the dose by 1 μg/kg every 2 weeks.
- If platelet count is > 400 x 10^9/L, do not dose. Continue to assess the platelet count weekly. After the platelet count has fallen to < 200 x 10^9/L, resume NPLATE at a dose reduced by 1 μg/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 x10^9/L or to a level sufficient to avoid clinically important bleeding after four weeks at the highest weekly dose of 10 μg/kg. Dosing requirements should be individualized according to the needs of each ITP patient. During the placebo controlled studies, 3 μg/kg (25th-75th percentile: 1-4 μg/kg) was the median most frequent dose administered to both splenectomized and nonsplenectomized patients to achieve a platelet count ≥ 50 x 10^9/L. In an open-label study of refractory patients with ITP who had failed numerous prior ITP therapies, 7 μg/kg (25th-75th percentile: 5-9.5 μg/kg) was the median most frequent dose administered to achieve the same platelet level. Therefore, while doses higher than 7 μg/kg are not required for most patients, a subgroup of the most severely ill patients may require higher maximum doses. Doses higher than 10 μg/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 ≥ 50 x 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: 375 μg/vial and 625 μg/vial. Each vial contains sufficient product to provide a deliverable dose of up to 250 μg and 500 μg, respectively, when reconstituted as instructed. See Table 9 below.

NPLATE (250 μg) single-use vial (containing 375 μg powder for solution for injection) should be reconstituted with 0.72 mL of Sterile Water for Injection USP, yielding a 500 μg/mL concentration (total extractable dose per vial is 250 μg in 0.5 mL). An additional overfill is included in each vial to ensure that 250 μg of romiplostim can be delivered (Table 9).

NPLATE (500 μg) single-use vial (containing 625 μg powder for solution for injection) should be reconstituted with 1.2 mL of Sterile Water for Injection USP, yielding a 500 μg/mL concentration (total extractable dose per vial is 500 μg in 1.0 mL). An additional overfill is included in each vial to ensure that 500 μg of romiplostim can be delivered (Table 9).

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 μg	375 μg	add	0.72 mL	=	250 μg in 0.5 mL	500 μg/mL
500 μg	625 μg	add	1.2 mL	=	500 μg in 1 mL	500 μg/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 colourless. Visually inspect the reconstituted solution for particulate matter and/or discolouration. Do not administer NPLATE if particulate matter and/or discolouration 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°C to 8°C (36°F 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*). 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 μg/mL):

Volume to Administer (mL) = Individual patient Dose (μg) / 500 μg/mL
(Round volume to the nearest hundredth mL)

For example, a 75 kg patient initiating therapy at 1 μg/kg will begin with a dose of 75 μg. For this patient example, the 75 μg dose is divided by 500 μg/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.

Administration Precautions

Caution should be used during preparation of NPLATE in calculating the dose and reconstitution with the correct volume of sterile water for injection. Special care should be taken to ensure that the appropriate volume of NPLATE is withdrawn from the vial for subcutaneous administration (see *Warnings and Precautions* and *Overdosage*).

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

In early clinical studies, the maximum dose of NPLATE (romiplostim) was 30 μg/kg. This was later reduced to 10 μg/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 μg/kg (500 times the maximum clinical dose of 10 μg/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 (see *Dosage and Administration* and *Warnings and Precautions*).

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 nonsplenectomized 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 μg/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 μg/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

		$AUC_{0\text{-}7day}$ (pg*hr/mL)		**C_{max} (pg/mL)**		**t_{max} (hour)**		**$t_{1/2}$ (hour)**		**Predose Platelet Count ($x\ 10^9$/L)**	
Subject	Dose μg/kg	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; $AUC_{0\text{-}7day}$ = 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 lyophilized product should be stored refrigerated at 2° C to 8°C (36°F to 46°F); vials should be kept in the original carton to protect from light until time of use. Do not freeze. Alternatively, NPLATE lyophilized product can be kept at room temperature up to 25°C (77°F) in the original carton; however, under these conditions, NPLATE lyophilized product must be used within 30 days. If not used within the 30 days, discard NPLATE.

Protect NPLATE from direct light and do not expose to temperatures above 25°C (77°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

NPLATE (romiplostim) is supplied as a sterile lyophilized solid white powder containing 375 μg or 625 μg NPLATE in single-dose vials for reconstitution.

Each NPLATE (250 μg) vial contains 375 μg 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 μg) vial contains 625 μg 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.

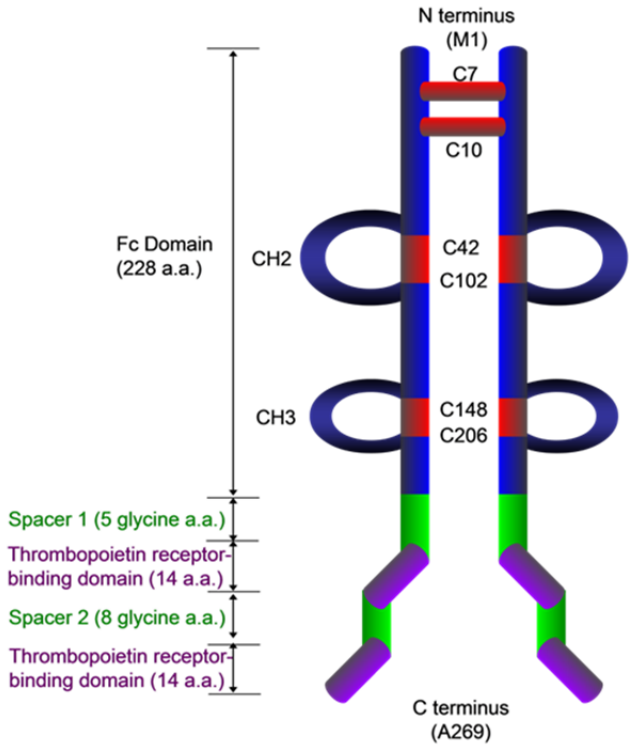
PART II: SCIENTIFIC INFORMATION

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 and one Phase 3 randomized, controlled, open-label study in adults with chronic ITP who had completed at least one treatment prior to study entry.

Placebo-Controlled Studies

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 x 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 x 10^9/L at study entry.

Entry criteria were the same in both of the placebo controlled studies except that patients in Study S1 had not undergone splenectomy while patients in Study S2 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 ≤ 30 x 10^9/L, with no individual count > 35 x 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 S2, splenectomy was required to have occurred at least 4 weeks before study entry.

Among patients enrolled into Study S2, 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.

Open-label Study (Study S3)

Use of NPLATE in NonSplenectomized ITP Patients compared with Standard of Care (SOC).

Study S3 (131) was a randomized 52 week trial of subjects who received NPLATE or medical SOC treatment. Medical SOC treatments, including the option of watchful waiting, were selected and prescribed by the investigator according to standard institutional practices or therapeutic guidelines. This study evaluated nonsplenectomized patients with ITP and platelet counts < 50 x 10^9/L. NPLATE was administered by subcutaneous (SC) injection once weekly starting at a dose of 3 μg/kg, and adjusted throughout the study within a range of 1-10 μg/kg in order to maintain platelet counts between 50 and 200 x 10^9/L.

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 μg/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 μg/kg SC weekly, adjusted by platelet count, for 24 weeks
Open-label Study						
Study S3 (131) [3,6]	A Randomized, Controlled, Open-label Study Evaluating the Efficacy and Tolerability of AMG 531 versus Medical Standard of Care (SOC) as Chronic Therapy for Nonsplenectomized Subjects with Immune (Idiopathic) Thrombocytopenia Purpura	Two primary endpoints: 1. The number of subjects undergoing a splenectomy during the 52-week treatment period by randomized treatment group. 2.The number of subjects with a treatment failure during the 52-week treatment period by randomized treatment group.	234 subjects: 157 NPLATE 77 SOC	18 to 90	White/Caucasian,, 206 Hispanic/Latino, 14 Black/African American, 6 Asian, 6 American Indian/Alaskan Native, 1 Other, 1 Men, 103 Women, 131	3.0 μg/kg SC weekly, adjusted by platelet count, for 52 weeks
Long-term extension study						

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
Study S4 (213)[4]	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	292 subjects 291 NPLATE	19 to 90	White, 246 Black, 13 Hispanic, 21 Asian, 9 Japanese, 1 American Indian/Alaska Native, 1 Native Hawaiian or other Islander, 1 Men, 108 Women, 184	1.0 to 30 µg/kg SC weekly, adjusted by platelet count; Maximum dose reduced to 15 µg/kg and then to 10 µg/kg

Study results

Placebo-Controlled Studies (Studies S1 and S2)

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 μg/kg or placebo. Patients received single weekly SC injections for 24 weeks. Doses were adjusted to maintain platelet counts (50 to 200 x 10^9/L).

In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response in the romiplostim treated patients compared to the placebo treated patients (defined as weekly platelet count ≥ 50 x 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 these placebo-controlled studies, the most frequently used weekly dose during weeks 17-24 for splenectomized patients was between 2-7 μg/kg (25th-75th percentile respectively; median 3 μg/kg) and for nonsplenectomized patients was between 1-3 μg/kg (25th-75th percentile respectively; median 2 μg/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.

Following discontinuation of NPLATE during studies S1 and S2, seven patients maintained platelet counts of ≥ 50 x 10^9/L until week 36, without requiring further treatment with NPLATE, and were therefore not enrolled in the long term extension study.

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

[a] Durable platelet response was defined as weekly platelet count ≥ 50 x 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.

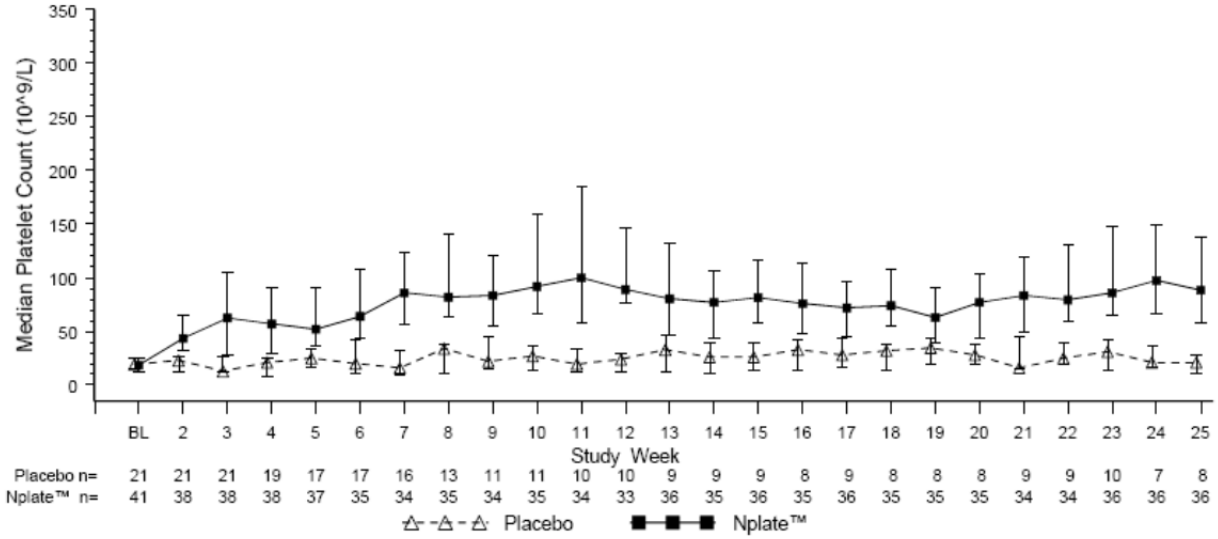
[c] Number of weeks with platelet response is defined as number of weeks with platelet counts ≥ 50 x 10^9/L during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medications.

[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 μg/kg during the last 8 weeks of treatment.

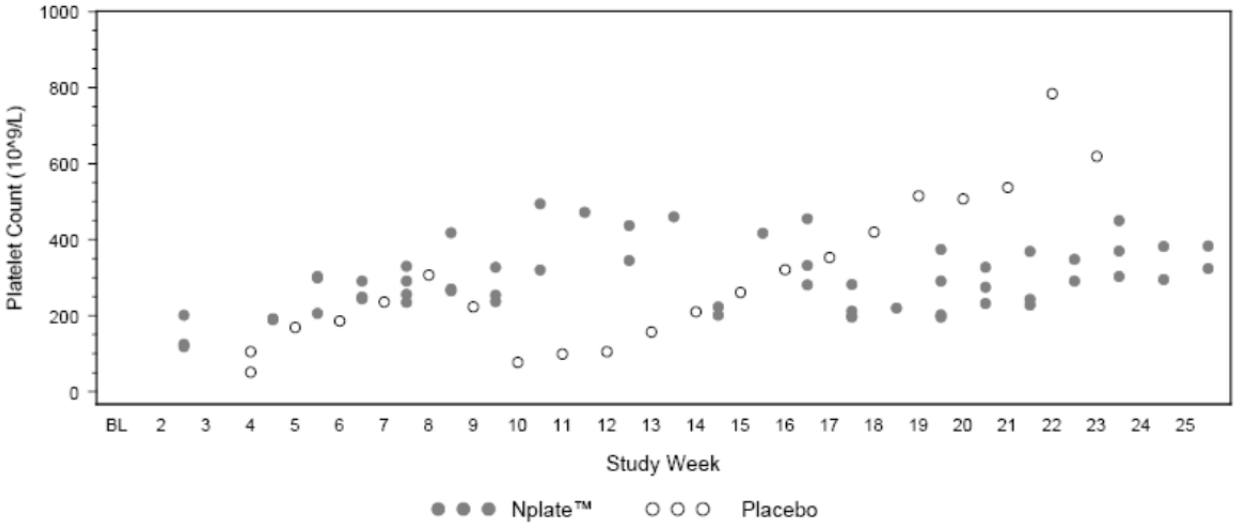
In both Phase 3, placebo-controlled studies, 50% to 70% of patients maintained platelet counts ≥ 50 x 10^9/L starting week 6 during the 24-week treatment period. In the placebo group, 0% to 7% of patients were able to achieve a platelet count response during the 6 months of treatment. Figure 3, Figure 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



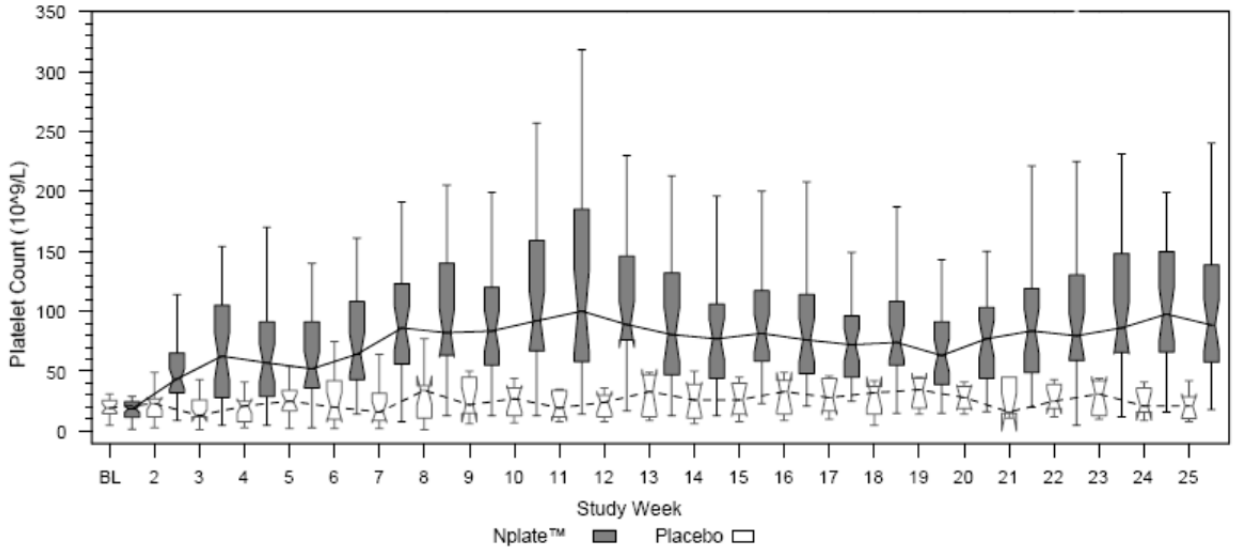
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use.
Baseline platelet value (BL) = mean of platelet counts at Days -8, -2 and pre-dose Day 1.

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



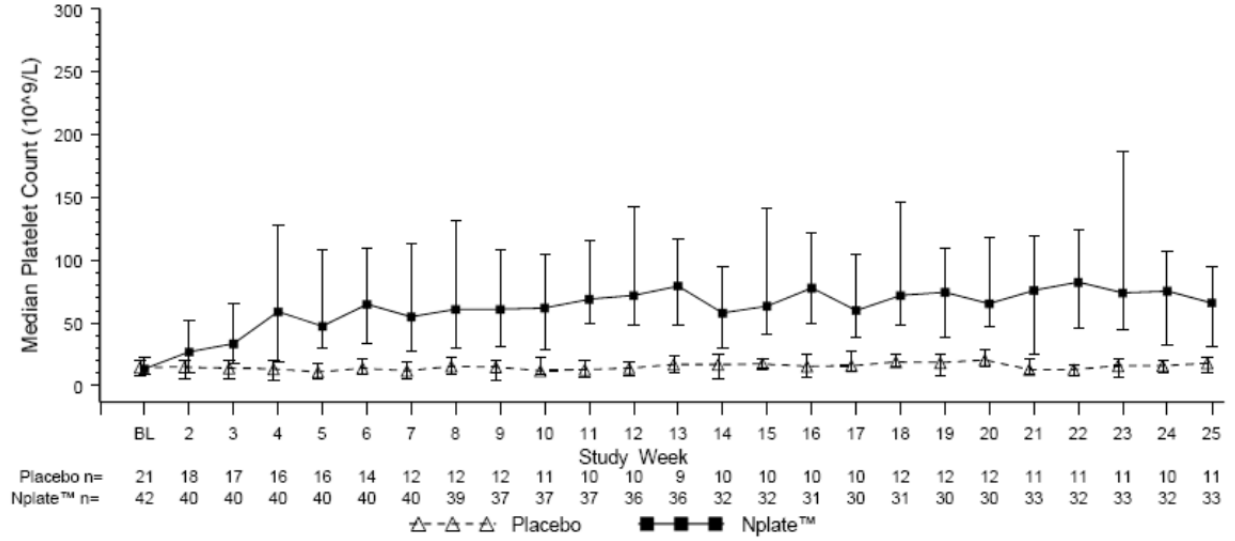
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use.
Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and pre-dose day 1.

Figure 5. Notched Box Weekly Platelet Counts in Nonsplenectomized Subjects



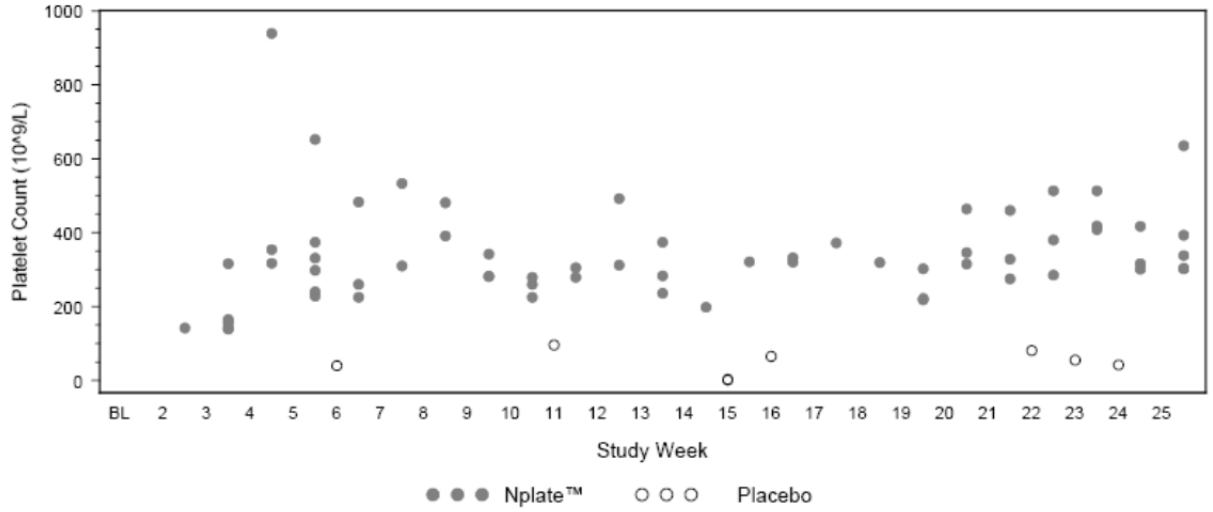
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use.
Whiskers represent the upper and lower adjacent values; top and bottom of box indicate inter-quartile range.
Baseline platelet value (BL) = mean of platelet counts at days -8, -2, and pre-dose day 1.

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



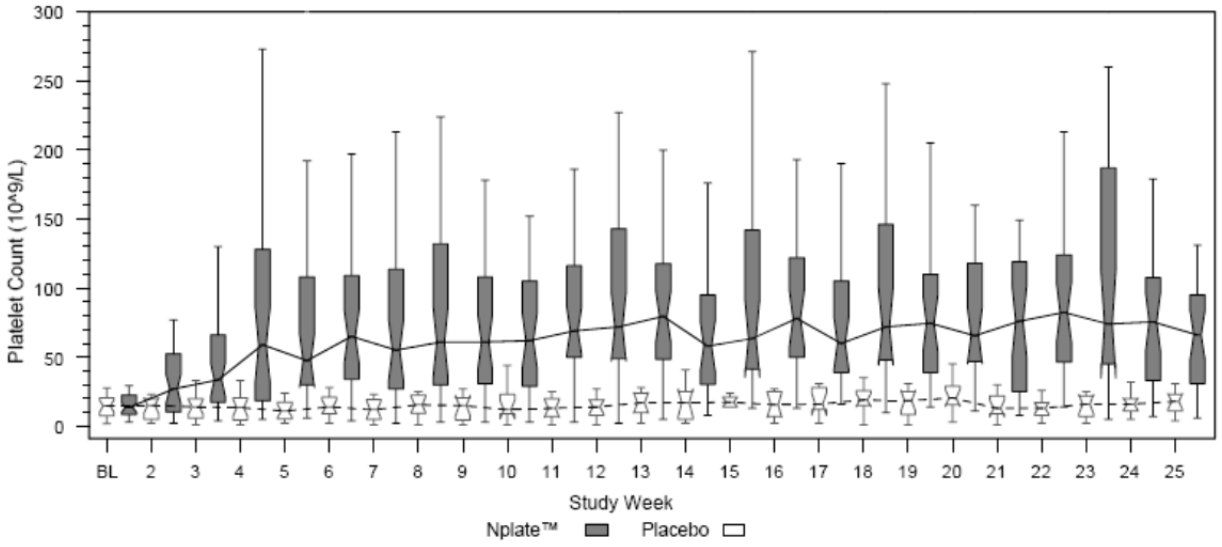
Includes all randomized patients excluding platelet counts within 8 weeks after rescue medication use.
Baseline platelet value (BL) = mean of platelet counts at Days -8, -2 and pre-dose Day 1.

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.

Open-label Study (Study S3)

Nonsplenectomized patients (≥ 18 years) were randomized in a 2:1 ratio to NPLATE or medical SOC for ITP if their platelet count was < 50 x 10^9/L or their platelet count fell to < 50 x 10^9/L during or after a clinically-indicated taper or discontinuation of current ITP therapy. NPLATE was administered by subcutaneous (SC) injection once weekly starting at a dose of 3 μg/kg, adjusted as needed throughout the study to a maximum dose of 10 μg/kg in order to maintain platelet counts between 50 and 200 x 10^9/L.

Of the 157 subjects randomized to receive NPLATE, the median (range) duration of exposure was 52.0 weeks (2 to 53). The median (25^{th}, 75^{th} percentiles) weekly dose of NPLATE was 3 μg/kg (3 to 5).

Table 13. Demographics
(Full Analysis Set)

	SOC (N = 77)	NPLATE (N = 157)	Total (N = 234)
Age Group in Years - n (%)			
18 - 29	9 (11.7)	20 (12.7)	29 (12.4)
30 - 39	8 (10.4)	18 (11.5)	26 (11.1)
40 - 49	14 (18.2)	21 (13.4)	35 (15.0)
50 - 59	10 (13.0)	28 (17.8)	38 (16.2)
60 - 69	15 (19.5)	30 (19.1)	45 (19.2)
70 - 79	14 (18.2)	30 (19.1)	44 (18.8)
≥ 80	7 (9.1)	10 (6.4)	17 (7.3)
≥ 65	29 (37.7)	54 (34.4)	83 (35.5)
≥ 75	13 (16.9)	29 (18.5)	42 (17.9)
Age (yrs)			
n	77	157	234
Mean	54.7	54.8	54.7
SD	19.3	18.8	18.9
Median	57.0	58.0	57.0
Q1, Q3	42.0, 70.0	42.0, 70.0	42.0, 70.0
Min, Max	18, 86	18, 90	18, 90
Sex - n (%)			
Female	46 (59.7)	85 (54.1)	131 (56.0)
Male	31 (40.3)	72 (45.9)	103 (44.0)
Race - n (%)			
White or Caucasian	69 (89.6)	137 (87.3)	206 (88.0)
Black or African American	0 (0.0)	6 (3.8)	6 (2.6)
Hispanic or Latino	5 (6.5)	9 (5.7)	14 (6.0)
Asian (e.g. Chinese, Bangladeshi, Indian, Pakistani)	1 (1.3)	5 (3.2)	6 (2.6)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	1 (1.3)	0 (0.0)	1 (0.4)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Aborigine	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.3)	0 (0.0)	1 (0.4)
Weight (kg)			
n	74	155	229
Mean	81.7	81.5	81.6
SD	22.9	19.4	20.6
Median	77.0	77.5	77.0
Q1, Q3	67.3, 90.5	68.2, 94.0	68.2, 92.0
Min, Max	45, 183	49, 143	45, 183

SOC = Standard of Care.
Full analysis set includes all randomized subjects.
Percentages are based on N.

Table 14. ITP Treatment History (Full Analysis Set)

	SOC (N = 77)	NPLATE (N = 157)	Total (N = 234)
Years since ITP Diagnosis[a]			
n	77	157	234
Mean	4.566	4.304	4.390
SD	5.669	6.135	5.974
Median	2.260	2.080	2.090
Q1, Q3	0.400, 6.540	0.460, 5.340	0.450, 5.890
Min, Max	0.01, 33.22	0.02, 44.22	0.01, 44.22
Number of Prior ITP Therapy[b] - n (%)			
1	17 (22.1)	47 (29.9)	64 (27.4)
2	28 (36.4)	53 (33.8)	81 (34.6)
3	16 (20.8)	35 (22.3)	51 (21.8)
≥ 4	16 (20.8)	22 (14.0)	38 (16.2)

SOC = Standard of Care.
Full analysis set includes all randomized subjects.
Percentages are based on N.
[a] Years are calculated as (randomization date - ITP diagnosis date) / 365.25. Partial dates of ITP diagnosis with missing day only are imputed as 15, partial dates with missing month and day are imputed as July 1.
[b] ITP treatments include: Corticosteroid, Anti-D Antibody, IV Immune Gamma Globulin, Vinscristine/Vinblastine, Danazol, Cyclophosphamide, Azathioprine, Rituximab, and other.

Table 15. Medical and Surgical History (Full Analysis Set)

	SOC (N = 77) n (%)	NPLATE (N = 157) n (%)	Total (N = 234) n (%)
Subjects with history related to any of:			
Special Senses	11 (14.3)	28 (17.8)	39 (16.7)
Cardiovascular	46 (59.7)	81 (51.6)	127 (54.3)
Dermatologic	18 (23.4)	34 (21.7)	52 (22.2)
Endocrine / Metabolic	34 (44.2)	61 (38.9)	95 (40.6)
Gastrointestinal	42 (54.5)	79 (50.3)	121 (51.7)
Genitourinary / Reproductive	31 (40.3)	63 (40.1)	94 (40.2)
Hematologic / Lymphatic	28 (36.4)	39 (24.8)	67 (28.6)
Hepatic / Biliary	21 (27.3)	32 (20.4)	53 (22.6)
Immunologic	12 (15.6)	21 (13.4)	33 (14.1)
Musculoskeletal	41 (53.2)	82 (52.2)	123 (52.6)
Neurologic / Psychiatric	30 (39.0)	49 (31.2)	79 (33.8)
Renal	10 (13.0)	21 (13.4)	31 (13.2)
Respiratory	26 (33.8)	51 (32.5)	77 (32.9)
Other	38 (49.4)	62 (39.5)	100 (42.7)

SOC = Standard of Care.
Full analysis set includes all randomized subjects.
Percentages are based on N.
Subjects may have multiple entries across categories, however, within each category, they are counted only once.

The median times to splenectomy and treatment failure were not reached. Based on post-hoc efficacy analyses, the Kaplan-Meier (KM) estimates of rate of splenectomy or death at the end of treatment are 42.1% in the SOC arm and 2.1% in the NPLATE arm. The KM estimates of rate of treatment failure or death at the end of treatment are 28.5% in the SOC arm and 4.8% in the NPLATE arm. However, the data show that a proportion of patients in the SOC arm (19 patients; 24.7%) did not receive any therapeutic intervention during the entire study, and imbalances in patient characteristics and rescue medications between the two arms were observed. For these reasons and due to the open-label nature of this trial and the addition of post-hoc efficacy analyses, the data should be interpreted cautiously.

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 x 10^9/L within a single week while also crossing 50 x 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 (ie, 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 16 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 16. Concurrent ITP Medical Therapies

	Study S1 Nonsplenectomized Patients		Study S2 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 for hemorrhage. 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 17 and Table 18).

Table 17. 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)
PREDNISONE	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 18. Subject Incidence of Rescue Medications (Splenectomized)

	NPLATE (N = 42) n (%)	Placebo (N = 21) 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 (Study S4)

Study S4 (213) was an open-label extension study with the secondary objective of assessing the durability of platelet count increases in subjects who had completed a previous NPLATE ITP study (including the Phase 3 studies). NPLATE was administered by SC injection once weekly starting either at the same dose received at the end of treatment 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 entering the extension study that had been off study drug for > 24 weeks started at a dose of 1μg/kg.

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.

Two hundred and ninety two adult subjects who completed their parent study were enrolled in the extension study S4 (213), and 291 subjects received at least 1 dose of NPLATE. By the third week after receiving NPLATE, the majority (73%) of subjects achieved a platelet response (platelet count $\geq 50 \times 10^9$/L without rescue medication use in the past 8 weeks). The responses were generally maintained throughout the remainder of the study with a median duration of NPLATE treatment of 78 weeks (range, 1 to 277 weeks).

One hundred fifty six of 282 adult subjects (55.3%) were able to maintain their dose within 2 μg/kg of the most frequent dose after the initial dose-adjustment period (12 weeks).The overall subject incidence of rescue medication use in adult subjects was 33.3%. Approximately 13% (37/291) of adult subjects were receiving concurrent ITP therapy at the time of study entry.

Twenty (54.1%) of these subjects discontinued concurrent ITP therapy by the end of the study. Of the 38 (13%) subjects who had bone marrow biopsies, no evidence of type I collagen was observed, however, the number of subjects with a bone marrow biopsy was low and trichrome staining for type I collagen was inconsistently performed on the samples.

Due to the single-arm open-label nature of this trial and 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 thrombopoetin (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

In rat and rabbit development toxicity studies, no evidence of fetal harm was observed at NPLATE exposures up to 11 times (rats) and 82 times (rabbits) higher than the maximum indicated human dose of 10 μg/kg (see *Dosage and Administration)*. In mice, at exposures 5 times higher than the maximum indicated human dose, there were reductions in maternal body weight and evidence of increased post implantation loss (see Table 19).

In a prenatal and postnatal development study in rats, at exposures 11 times the maximum indicated human dose, there was a slight increase in the incidence of peri-natal pup mortality.

NPLATE is known to cross the placental barrier in rats at clinically relevant or higher doses.

Animal Toxicology and/or Pharmacology

In a 4-week repeat dose toxicity study in rats, NPLATE caused bone hyperosteosis 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 19). 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 19. 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 μg/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-μg/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-μg/kg and 1000-μg/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 μg/kg SC; 100 μg/kg IV; TIW x 4 wk Additional 12/sex/group used in TK evaluations Additional 20/sex/group used in platelet aggregation studies	10/sex/group necropsied after 1 month treatment 5/sex/group (0 and 100 μg/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-μg/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-μg/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 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.

Table 19. Summary of Toxicology Studies with NPLATE

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
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 µg/kg (IV and SC); 500, 1000 µg/kg (SC); 5000 µg/kg (IV and SC); TIW x 4 wk	3/sex/group necropsied after 1 month treatment 2/sex/group (0 µg/kg and 5000 µg/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.
Four-week Repeated Dose Toxicity Study of Subcutaneous NPLATE Administered to Female Cynomolgus and Rhesus Monkeys Followed by a 4-week Recovery Period	Female cynomolgus monkeys n = 32 (6 or 8 F/group, as indicated in Design column): 0, 100, 300, 500, 5000 µg/kg SC; TIW x 4 wk Female rhesus monkeys n = 16 (8F/group): 0, 5000 µg/kg SC; TIW x 4 wk	4/group necropsied after 1 month treatment (exception = n of 5 for the 5000-µg/kg group); 2/group necropsied after 1 month treatment and 1 month recovery (exception = n of 3 for the 5000-µg/kg group) 5/group necropsied after 1 month treatment; 3/group necropsied after 1 month treatment and 1 month recovery	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-µg/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.

Table 19. Summary of Toxicology Studies with NPLATE

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
Three- and 6-Month Toxicology Study of Repeated Administration of Subcutaneous NPLATE in Cynomolgus Monkeys	Cynomolgus monkeys n = 64 (8/sex/group): 0, 500, 1000, 5000 μg/kg SC; QW x 3 or 6 mo	3/sex/group necropsied at week 13 3/sex/group necropsied at week 26 2/sex/group necropsied at week 34	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-μg/kg groups, and megakaryocytosis in the submandibular lymph nodes in the 1000-μg/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 μg/kg in this study. TK of NPLATE was linear with dose in the range of 500 to 5000 μg/kg 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 μg/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-μg/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-μg/kg groups. Enlarged spleens were observed in the 30- and 100-μg/kg groups. Treatment with NPLATE had no effect on fertility. The lowest observable adverse effect level was 30 μg/kg due to effects on body weight and food consumption. The NOAEL was 10 μg/kg.

Table 19. Summary of Toxicology Studies with NPLATE

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
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 μg/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-μg/kg group compared with the control group for days 0 to 18. The greatest weight gain decease, 53.8% relative to control animals, occurred during GD 6 to 9 in the 100-μg/kg group. Maternal body weights and body weight gains were unaffected by doses up to 30 μg/kg. Seven to 8 pregnant females had ≥ 1 live fetus per dose group. The number of resorptions increased in the 3.0- and 100-μg/kg groups (1.5- and 2.3-fold, respectively, versus controls). Most resorptions were early resorptions. Average live litter size was reduced in the 100-μg/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 μg/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 μg/kg SC Additional 15F/group (0, 10, 30, 100 μg/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 μg/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 μg/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 μg/kg.

Table 19. Summary of Toxicology Studies with NPLATE

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
Embryo-fetal Development Study of AMG NPLATE 531 in New Zealand White Rabbits	New Zealand White rabbits (mated females) n = 25 (5F/group): 0, 10, 30, 60, 100 μg/kg SC Additional 3F/group (0, 10, 30, 100 μg/kg) used for TK evaluation	Dosed on GD7, 9, 11, 13, 15, 17, and 19 Euthanized on GD30	Treatment with NPLATE had no effect on maternal mortality, clinical observations, maternal body weight, gross pathology, pregnancy status, gravid 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-μg/kg group than in control animals. Mean food consumption was sporadically lower in the 100-μg/kg group. One fetus in the 100-μg/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.
Study of the Prenatal and Postnatal Development and Maternal Function in Rats After Subcutaneous Injection of NPLATE	Sprague-Dawley rats (females) n = 176 (44/group): 0, 10, 30, 100 μg/kg SC	Dosed every other day beginning GD6 to PND 20 or 21 F1 generation assessed for functional behavior and mating function	Four F_0 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 F_0 females that did not develop anti- NPLATE antibodies was approximately 4-fold higher than 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. The mean length of gestation was slightly increased in females receiving NPLATE at all dose levels (22 days) relative to the

Table 19. Summary of Toxicology Studies with NPLATE

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
			mean length of gestation in the controls (21 days). The live-birth index was decreased for females in the 100-µg/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. Splenic enlargement was noted in the majority of F_0 females in the 100-µg/kg group and in a single F_0 female in the 30-µg/kg group. No other differences were noted in the necropsy observations or reproductive organ weights that were related to treatment with NPLATE. Slight prolongation of gestation was observed for F_0 females in all NPLATE groups. There was no definitive NOAEL for effects of NPLATE on F_0 gestation in this study. Based on the slightly increased perinatal pup mortality in the 100-µg/kg group, NOAEL for prenatal and postnatal physical and functional development of the F_1 offspring was determined to be 30 µg/kg.
Other Studies – Safety Pharmacology			
Study of the Pharmacologic Effects of a Single SC Dose of NPLATE on Central Nervous System of Sprague-Dawley Rats	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 µg/kg SC	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	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-µg/kg group, the concentration of NPLATE was below the LLOQ. Due to limited sampling, TK profiles were not well characterized in this study.

Table 19. Summary of Toxicology Studies with NPLATE

Title	Species/Dosing (n)	Design	Significant Results/Conclusions
Cardiovascular Evaluation of AMP2 in Cynomolgus Monkeys Via Bolus Intravenous Injection	Cynomolgus monkeys n = 12 (3M/group): 0, 500, 1000, 5000 μg/kg IV	Single dose; no necropsy done	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-μg/kg groups, respectively. The platelet counts for the 5000-μg/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.
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 μg/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 μg/kg SC given approximately every 21 days for 4 cycles Single SC administration at 50 μg/kg Doses of 50, 100, 500, 1000 μg/kg SC were administered approximately every 21 days for 6 cycles after the initial dose of 50 μg/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.

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PART III: CONSUMER INFORMATION

[Pr]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 MEDICATION

What 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 625 micrograms or 375 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 have or have had any of the following medical conditions
  - liver problems
  - kidney problems
  - blood clots or if blood clots are common in your family (The risk of blood clotting may also be increased if you have liver problems, are elderly ($\geq$ 65 years), are bedridden, have cancer, are taking the contraceptive pill or hormone replacement therapy, have recently had surgery or suffered an injury, are obese (overweight), are a smoker)
- you are pregnant; think you may be pregnant; or plan to get pregnant. NPLATE has not been tested in pregnant women.

Women who become pregnant during NPLATE treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-866-512-6436 to enroll.

Care should be taken if you are breast-feeding, as it is not known whether NPLATE is present in human milk. Women who are breastfeeding during NPLATE treatment are encouraged to enroll in Amgen's Lactation Surveillance Program. Patients or their physicians should call 1-866-512-6436 to enroll.

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 reticulin." 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) or bleeding events 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. You may have severe complications or die from some forms of blood clots, such as clots that spread to the lungs or that cause heart attacks or strokes. If you have a chronic liver disease, you may get blood clots in the veins of your liver. This may affect your liver function. Your doctor will adjust your dose of NPLATE to ensure that your platelet count does not become too high.

Your doctor will determine the right amount of NPLATE that you should receive. If you have been given more NPLATE than you should, you may not experience any physical symptoms but your blood platelet counts may rise to very high levels and this may increase the risk of blood clotting. If you have been given less NPLATE than you should, you may not experience any physical symptoms but your blood platelet counts may become low and this may increase the risk of bleeding. Therefore if your doctor suspects that you have been given more or less NPLATE than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

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). Special care should be taken to ensure the appropriate volume of NPLATE is withdrawn from the vial.

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.

Tell your healthcare provider about any bruising or bleeding that occurs while you are receiving NPLATE.

Overdose:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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 should be prepared by carefully calculating the dose and reconstituting with the correct volume of sterile water for injection.

Each vial of Nplate 250 micrograms powder for solution for injection contains a total of 375 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 250 micrograms of romiplostim can be delivered. After reconstitution (dissolving) with 0.72 mL of sterile water for injection, a deliverable volume amount of 0.5 mL solution contains 250 micrograms of romiplostim (500 micrograms/mL).

Each vial of Nplate 500 micrograms powder for solution for injection contains a total of 625 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 500 micrograms of romiplostim can be delivered. After reconstitution (dissolving) with 1.2 mL of sterile water for injection, a deliverable volume amount of 1 mL solution contains 500 micrograms of romiplostim (500 micrograms/mL).

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 unwanted effects.

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

- aching joints (arthralgia)
- muscle aches (myalgia)
- pain in extremity
- headache
- dizziness
- difficulty sleeping (insomnia)

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

- abdominal pain
- low blood platelet count (thrombocytopenia) after stopping NPLATE
- shoulder pain
- tingling or numbness of the hands or feet (paresthesia)
- upset stomach (dyspepsia)
- higher than normal platelet counts (thrombocytosis)
- hypersensitivity
- bleeding (hemorrhage)

Uncommon side effects (seen in more than 1 in 1000, but less than 1 in 100 people taking NPLATE):

- increased fibers (reticulin) in the bone marrow (bone marrow reticulin fibrosis)
- redness, heat and pain of skin (erythromelalgia)
- hive-like swelling beneath the skin (angioedema)

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

Symptom / effect[a]		Talk with your doctor		Call your doctor
		Only if severe	In all cases	
Very common (seen in more than 1 in 10 people)	Headache		√	Headache may be a symptom of a blood clot.
Common (seen in more than 1 in 100, but less than 1 in 10 people)	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.
	Higher than normal platelet counts (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.
Uncommon (seen in more than 1 in 1000, but less than 1 in 100 people)	Increased fibers (reticulin) in the bone marrow (bone marrow reticulin fibrosis)		√	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.
	Angioedema		√	You may potentially experience hive-like swelling beneath the skin. Contact your doctor immedicately.

[a] Frequency reflects all adverse events (serious and non-serious)

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.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

Alternatively, unreconstituted vials of this medicine may be removed from the refrigerator for a period of up to 30 days in the original carton;

- If removed from the refrigerator, this medicine must be used within 30 days.
- If not used within the 30 days, discard NPLATE.

Do not freeze.

Store in original carton in order to protect from light and do not expose to temperatures above 25°C (77°F).

Do not use NPLATE after the expiry date which is stated on the carton and vial label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Amgen Canada Inc. at: 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

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