▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – NPLATE® (ROMIPLOSTIM)

1. NAME OF THE MEDICINE

Romiplostim.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nplate contains the active ingredient, romiplostim.

It is supplied as a sterile, preservative-free, lyophilized white powder in single dose glass vials for reconstitution and subcutaneous (SC) injection.

230 microgram powder for injection

Each vial contains 230 micrograms (µg) of romiplostim.

After reconstitution, a deliverable volume of 0.25 mL of solution contains 125 µg of romiplostim (500 µg/mL). An overfill is included in each vial to ensure that 125 µg can be drawn from the vial.

375 microgram powder for injection

Each vial contains 375 micrograms (µg) of romiplostim.

After reconstitution, a deliverable volume of 0.5 mL of solution contains 250 µg of romiplostim (500 µg/mL). An overfill is included in each vial to ensure that 250 µg can be drawn from the vial.

625 microgram powder for injection

Each vial contains 625 micrograms (µg) of romiplostim.

After reconstitution, a deliverable volume of 1 mL of solution contains 500 µg of romiplostim (500 µg/mL). An overfill is included in each vial to ensure that 500 µg can be drawn from the vial.

Excipient(s) with known effect

Nplate contains mannitol and sucrose.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Nplate is a sterile, white, preservative-free, lyophilised powder for reconstitution and administration as a subcutaneous (SC) injection.

The reconstituted solution should be clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Nplate is indicated for treatment of thrombocytopenia in adult patients with primary immune thrombocytopenia (ITP) who are:

- non-splenectomised and have had an inadequate response, or are intolerant, to corticosteroids and immunoglobulins;
- splenectomised and have had an inadequate response to splenectomy.

Paediatrics

Nplate is indicated for treatment of thrombocytopenia in paediatric patients aged 1 year and older with primary immune thrombocytopenia ITP for at least 6 months who are:

- non-splenectomised and have had an insufficient response, or are intolerant, to corticosteroids and immunoglobulins;
- splenectomised and have had an inadequate response to splenectomy.

4.2 Dose and method of administration

Treatment should be under the guidance of an experienced healthcare provider.

Use the lowest dose of Nplate necessary to achieve and maintain a platelet count ≥ 50 x 10^9/L. Administer Nplate as a weekly subcutaneous injection, with dose adjustments based upon the platelet count response.

The prescribed Nplate dose may consist of a very small volume (e.g. 0.15 mL). Administer Nplate using a syringe with 0.01 mL graduations only.

Discontinue Nplate if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks at the highest weekly dose of 10 µg/kg.

Dosage (dose and interval)

Recommended dosage regimen

Initial dose

The recommended initial dose for Nplate is 1 µg/kg, based on actual patient's body weight.

Method of administration

For subcutaneous use. See Reconstitution instructions.

Patients who have a stable platelet count ≥ 50 x 10^9/L for at least 4 weeks without dose adjustment may, at the discretion of the supervising experienced healthcare provider, self-administer Nplate. Patients eligible for self-administration of Nplate should be trained in these procedures.

After the first 4 weeks of self-administration, the patient should again be supervised while reconstituting and administering Nplate. Only patients who demonstrate the ability to reconstitute and self-administer Nplate should be allowed to continue doing so.

Self-administration of Nplate is not recommended in children.

Dosage adjustment

Adjust the weekly dose of Nplate in increments of 1 µg/kg until the patient achieves a platelet count between 50 x 10^9/L to ≤ 200 x 10^9/L.

Assess the platelet count weekly until a stable platelet count (≥ 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved. Obtain platelet counts monthly thereafter. Dose adjustment recommendations are given in Table 1 and Table 2 for Adult and Paediatric patients respectively.

Do not exceed a maximum weekly dose of 10 µg/kg.

Table 1. Adult dose adjustment guidance based on platelet count

Platelet Count (x 10^9/L)	**Action**
Initial dose only is 1 µg /kg based on the patient's actual body weight	
< 50	Increase dose by 1 µg/kg.
> 200 for 2 consecutive weeks	Reduce the dose by 1 µg/kg.
> 400	Do not dose. Continue to assess the platelet count weekly. Reinitiate therapy when the platelet count is < 200 x 10^9/L at a dose reduced by 1 µg/kg.
If treatment is interrupted and platelet counts fall, reinitiate therapy at the previous dose of Nplate. If the patient loses response, see section 4.4 Special warnings and precautions for use, Loss of response to Nplate.	

Table 2. Paediatric and adolescent dose adjustment guidance based on platelet count

Platelet Count (x 10^9/L)	**Action**
Initial dose is 1 µg/kg, based on the patient's actual body weight	
< 50	Increase dose by 1 µg/kg.
50 to 200	Dose remains constant
> 200 to < 400 for 2 consecutive weeks	Reduce the dose by 1 µg/kg.
≥ 400	Do not dose. Reinitiate therapy when platelet count is < 200 x 10^9/L. Consider reducing dose by 1 µg/kg on thenext scheduled dosing day. Consider maintaining the dose Nplate if the platelet count increase was due to the initiation or increase in dose of a concurrentlyadministered ITP medication.
If treatment is interrupted and platelet counts fall, reinitiate therapy at the previous dose of Nplate. If the patient loses response, see section 4.4 Special warnings and precautions for use, Loss of response to Nplate.	

Dosage calculation

The volume administered is calculated based on body weight, dose required and concentration of product (see Table 3).

Table 3. Guidelines for calculating individual patient doses and volumes of Nplate to administer

Individual Patient Dose	**Individual Patient Dose (µg) = Weight (kg) x Dose in µg/kg** Actual body weight at initiation of treatment should always be used when calculating initial dose. In **adults**, future dose adjustments are based onchanges in platelet counts only. In **paediatric patients**, future dose adjustments are based on changes in platelet counts and **changes in body weight**. Reassessment of body weight is recommended every 12 weeks.

If Individual Patient Dose ≥ 23 µg	**Reconstitute** lyophilised product as described in section 4.2 Dose and method of administration, Reconstitution. The resulting concentration is 500 µg /mL. Volume to Administer (mL) = Individual patient dose (µg)/500 µg /mL (Round volume to the nearest 0.01 mL)
If Individual Patient Dose < 23 µg	Dilution is required to ensure accurate dosing. **Reconstitute** lyophilised product as described in section 4.2 Dose and method of administration, Reconstitution **and then dilute** the product as described in section 4.2 Dose and method of administration, Dilution. The resulting concentration is 125 µg/mL. Volume to Administer (mL) = Individual patient dose (µg)/125 µg/mL (Round volume to the nearest 0.01 mL)
Example	10 kg patient is initiated at 1 µg /kg of romiplostim. Individual patient dose (µg) = 10 kg x 1 µg /kg = 10 µg Because the dose is < 23 µg dilution is required to ensure accurate dosing. Reconstitute lyophilised product as described in section 4.2 Dose and method of administration, Reconstitution and then dilute the product as described in Section 4.2 Dose and method of administration, Dilution. The resulting concentration is 125 µg/mL. Volume to Administer (mL) = 10 µg/125 µg /mL = 0.08 mL

Treatment discontinuation

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician.

The recurrence of thrombocytopenia should be expected upon discontinuation of treatment (see section 4.4 Special warnings and precautions for use, Recurrence of thrombocytopenia after cessation of treatment).

Use of Nplate with concomitant medical ITP therapies

Medical ITP therapies used in combination with Nplate in clinical studies included corticosteroids, danazol, azathioprine, normal immunoglobulin (IVIG), and anti-D Rho immunoglobulin. If the patient's platelet count is > 50 x 10^9/L, other medical ITP therapies may be reduced or discontinued (see sections 5.1 Pharmacodynamic properties, Reduction in permitted concurrent ITP medical therapies and 4.5 Interactions with other medicines and other forms of interactions).

Reconstitution

Reconstitute only with Sterile Water for Injections as outlined in Table 4**.** Do not use saline or bacteriostatic water for injection, when reconstituting the product.

Table 4. Reconstitution of Nplate single use vials

Presentation	Total amountof romiplostim per vial		Sterile Water for Injections		Extractable Product and Volume	Final Concentration
125 µg/0.25 mL	230 µg	add	0.44 mL	=	125 µg in 0.25 mL	500 µg/mL
250 µg/0.5 mL	375 µg	add	0.72 mL	=	250 µg in 0.50 mL	500 µg/mL
500 µg/1 mL	625 µg	add	1.2 mL	=	500 µg in 1.0 mL	500 µg/mL

As the injection volume may be very small, a syringe with graduations to 0.01 mL should be used.

Gently swirl and invert the vial to reconstitute. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. Generally, dissolution of Nplate takes less than 2 minutes (see section 3 Pharmaceutical form).

Dilution

A dilution is required when the calculated individual patient dose is less than 23 µg.

Initial reconstitution of Nplate with designated volumes of sterile Water for Injections results in a concentration of 500 µg/mL (see Table 4). If the calculated individual patient dose is less than 23 µg (see section 4.2 Dose and method of administration), then **dilute reconstituted Nplate to 125 µg/mL with preservative-free, sterile, 0.9% sodium chloride.** This dilution step is required to ensure accuracy in preparation (see Table 5).

Table 5. Dilution Guidelines

Presentation	Add this volume of preservative-free, sterile sodium chloride 9 mg/mL (0.9%) solution for injection to the reconstituted vial	Concentration afterdilution
125 µg/0.25 mL	1.38 mL	125 µg/mL
250 µg/0.5 mL	2.25 mL	125 µg/mL
500 µg/1.0 mL	3.75 mL	125 µg/mL

See section 6.2 Incompatibilities and 6.4 Special precautions for storage conditions.

Administration precautions

Caution should be used during preparation of Nplate, both in calculating the dose and in reconstitution with the correct volume of sterile Water for Injections.

Special care should be taken to ensure that the appropriate volume of Nplate is withdrawn from the vial for subcutaneous administration (see sections 4.4 Special warnings and precautions for use, Medication errors and 4.9 Overdose).

Parenteral drug products, including Nplate solution, should be inspected visually for particulate matter and/or discolouration prior to administration. Do not use the contents of the container if any particulates or discolouration are observed.

Nplate must be used within:

- 24 hours of reconstitution and/or
- 4 hours of dilution.

See section 6.4 Special precautions for storage.

Each Nplate vial is for single use in one patient only. Discard any residue.

Do not add other medications to solutions containing Nplate.

4.3 Contraindications

Nplate is contraindicated in patients with known hypersensitivity to *E. coli*-derived products, romiplostim, or any other product ingredient (see section 6.1 List of excipients).

4.4 Special warnings and precautions for use

General

See Administration precautions in section 4.2.

Nplate should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk of bleeding. Nplate should not be used in other clinical conditions associated with thrombocytopenia.

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

Recurrence of thrombocytopenia after cessation of treatment

Thrombocytopenia is likely to recur upon discontinuation of Nplate; some patients may develop thrombocytopenia of greater severity than was present prior to Nplate. There is 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 complete blood counts (CBCs) be obtained for at least 2 weeks and alternative ITP treatment for worsening thrombocytopenia be considered according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support.

Serious life-threatening or fatal bleeding events after discontinuation of Nplate have been reported.

Increased bone marrow reticulin

Reticulin has been observed in the bone marrow of some ITP patients prior to treatment with Nplate and appeared to increase in some patients treated with Nplate. Increased bone marrow reticulin is believed to be due to the increased number of megakaryocytes in the bone marrow which may subsequently release cytokines. In clinical studies with Nplate, reticulin has not been associated with adverse clinical sequelae, cases of chronic idiopathic myelofibrosis (CIMF), or secondary myelofibrosis, and may improve upon discontinuation of Nplate.

Increased reticulin can be detected through bone marrow biopsy and may be suggested by morphological changes in the peripheral blood cells.

Prior to and during treatment with Nplate, examine peripheral blood smears and complete blood counts for new or worsening morphological abnormalities (e.g. teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If a patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Nplate and consider performing a bone marrow biopsy, with appropriate staining for fibrosis. Cytogenetic analysis of the bone marrow sample for clonal abnormality should also be considered.

The long-term risk for progression to myelofibrosis is unknown.

Thrombotic/Thromboembolic complications

Platelet counts above the normal range present a theoretical risk for thrombotic/thromboembolic complications. The incidence of thrombotic/thromboembolic events observed in the control groups were comparable to Nplate in clinical studies. No association between these events and

elevated platelet counts was observed. Dose adjustment guidelines should be followed (see section 4.2 Dose and method of administration).

In the post-marketing setting, thrombotic/thromboembolic events have been observed (see section 4.8 Adverse effects (Undesirable effects), Post-marketing experience).

To minimise the risk for thrombocytosis, do not use Nplate in an attempt to “normalise” platelet counts. Follow the dose adjustment guidelines to achieve and maintain a platelet count of ≥ 50 x 10^9/L (see section 4.2 Dose and method of administration).

Cases of thromboembolic events including portal vein thrombosis have been reported in patients with chronic liver disease receiving Nplate. Nplate should be used with caution in this population.

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

Risk of progression of myeloid malignancies or existing myelodysplastic syndromes (MDS)

TPO receptor stimulators are haematopoietic growth factors that lead to thrombopoietic progenitor cell expansion, differentiation, and platelet production. The TPO receptor is predominantly expressed on the surface of cells of the myeloid lineage; there is no confirmed expression of the TPO receptor on solid tumours. TPO has been shown to stimulate the proliferation of a subset of acute myeloblastic leukaemia cells in vitro. There is therefore a theoretical concern that romiplostim may stimulate the progression of existing myeloid malignancies or MDS.

In clinical studies of treatment with Nplate in adult patients with MDS, cases of progression to acute myeloid leukaemia (AML), a potential clinical outcome of MDS, were reported. In addition, there were cases of transient blast cell increases, which did not progress to AML. The risk-benefit profile for Nplate has not been established in MDS or other non-ITP patient populations.

A randomised, double-blind, placebo-controlled trial enrolling patients with severe thrombocytopenia and International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS was terminated due to more cases of AML observed in the Nplate treatment arm. This trial consisted of a 58-week study period with a 5-year long-term follow-up phase. The subjects were randomised 2:1 to treatment with Nplate or placebo (167 Nplate, 83 placebo). During the 58-week study period, progression to AML occurred in 10 (6.0%) subjects in the Nplate arm and 4 (4.8%) subjects in the placebo arm (hazard ratio [95%CI] = 1.20 [0.38, 3.84]). Of the 250

subjects, 210 (84.0%) entered the long-term follow-up phase of this study. With 5-years of follow-up, 29 (11.6%) subjects showed progression to AML, including 20/168 (11.9%) subjects in the Nplate arm versus 9/82 (11.0%) subjects in the placebo arm (HR [95% CI] = 1.06 [0.48, 2.33]). The incidence of death (overall survival) was 55.7% (93/167) in the Nplate arm versus 54.2% (45/83) in the placebo arm (HR [95% CI] = 1.03 [0.72, 1.47]). In the baseline low IPSS group, there was a higher incidence of death in the Nplate arm [41.3% (19/46)] compared to the placebo arm [30.4% (7/23)] [HR (95% CI) = 1.59 (0.67, 3.80)].

In a single arm trial of Nplate given to 72 subjects with thrombocytopenia-related MDS, 8 (11.1%) subjects were reported as having possible disease progression, of which 3 (4.2%) had confirmation of AML during follow up. In addition, in 3 (4.2%) subjects, increased peripheral blood blast cell counts decreased to baseline after discontinuation of Nplate.

Loss of response to Nplate

A loss of response or failure to maintain a platelet response with Nplate should prompt a search for causative factors including neutralising antibodies to Nplate (see section 4.8 Adverse effects (Undesirable effects), Immunogenicity) and increased bone marrow reticulin (see section 4.4 Special warnings and precautions for use, Increased bone marrow reticulin).

Medication errors

Medication errors including overdose and underdose have been reported in patients receiving Nplate. In some paediatric patients, accurate dosing relies on an additional dilution step after reconstitution (see section 4.2 Dose and method of administration, Dilution). 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 sections 4.4 Special warnings and precautions for use, Thrombotic/Thromboembolic complications, 4.2 Dose and method of administration and 4.9 Overdose).

Use in hepatic or renal impairment

Experience is limited in patients with severe hepatic or renal impairment. Nplate should be used with caution in these populations. Thromboembolic events have been reported in patients with chronic liver disease receiving Nplate (see section 4.4 Special warnings and precautions for use, Thrombotic/Thromboembolic complications).

Use in the elderly

Of 204 patients who received Nplate in ITP clinical studies, 38 (19%) were ≥ 65 years, and 18

(9%) were ≥ 75. No overall differences in safety or efficacy were observed between older and younger patients in the placebo-controlled studies, but greater sensitivity of older individuals cannot be ruled out.

Paediatric use

The safety and efficacy of Nplate in paediatric patients aged 1 year and older were evaluated in two randomised, placebo-controlled studies: a Phase I/II (Study 5) and a Phase III study (Study 4).

Similar to data from the adult ITP trials, Nplate induced high rates of durable and overall platelet response with a similar safety profile in children with symptomatic immune thrombocytopenia of more than 6 months duration.

Effects on laboratory tests

No interactions with laboratory and diagnostic tests have been identified.

4.5 Interactions with other medicines and other forms of interactions

No formal drug-drug interaction studies of Nplate have been performed.

ITP medical therapies used in combination with Nplate in clinical studies included corticosteroids, danazol, and/or azathioprine, normal immunoglobulin (IVIG) and anti-D Rho immunoglobulin.

Platelet counts should be monitored when combining Nplate with other ITP medical therapies in order to avoid platelet counts outside of the recommended range (see section 4.2 Dose and method of administration).

4.6 Fertility, pregnancy and lactation

Effects on fertility

Romiplostim had no observed effect on the fertility of male and female rats at subcutaneous doses up to 100 µg/kg administered 3 times weekly (up to 9 times the serum AUC in humans at the maximum recommended clinical dose). The predictive value of this animal study is limited, however, due to the frequent development of drug-neutralising antibodies.

Use in pregnancy

Pregnancy Category: B3

The safety and efficacy of romiplostim in pregnant women has not been established

Embryo-foetal development studies showed no increase in foetal abnormalities in rats given subcutaneous doses of romiplostim of up to 100 µg/kg every second day during gestation (up to 3 times the serum AUC in humans at the maximum recommended clinical dose). The predictive

value of these studies is limited, though, by the low animal: human exposure level and the development of drug-neutralising antibodies in the species. In a pre- and post-natal development study in rats, stillbirths were increased and perinatal pup survival was decreased at this dose level. An increase in post-implantation loss was observed in mice receiving a subcutaneous dose of 100 µg/kg every third day.

Romiplostim crosses the placenta in rats and maternal transmission to the developing foetus may occur in humans.

There are no studies with romiplostim in pregnant women. Nplate should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Patients who use romiplostim during pregnancy or become pregnant while receiving this drug are encouraged to enrol in Amgen's Pregnancy Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (free call within Australia).

Use in lactation

It is not known whether romiplostim is present in human milk. Many drugs are present in human milk and because of the potential for adverse effects in breastfed infants from romiplostim, a decision should be made to discontinue breastfeeding or discontinue the drug, taking into account the potential benefit of the drug to the mother or the potential benefit of breastfeeding to the infant.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed with Nplate. Patients should be informed that in clinical trials mild to moderate, transient bouts of dizziness were experienced by some patients

4.8 Adverse effects (Undesirable effects)

Summary of safety profile

Adverse events reported in fifteen ITP clinical trials are shown in Table 6. Based on an analysis of patients enrolled in four placebo-controlled studies, in one SOC-controlled study, and ten uncontrolled studies adverse events were reported in 1016 (94.2%) patients receiving Nplate (n=1078, including 104 paediatric patients) and in 129 (93.5%) patients receiving placebo/SOC (n=138, including 5 paediatric patients). The majority of these events were mild to moderate in nature, with severe, life-threatening or fatal adverse events reported in 38.4% of patients receiving placebo/SOC and in 39.6% of patients receiving Nplate.

The most commonly reported adverse events were headache, nasopharyngitis and arthralgia.

Table 6. Adverse Events Reported in ≥ 5% incidence in ITP Patients administered Nplate or Placebo/SOC by System Organ Class and Preferred Term (ITP Safety Set 15 ITP clinical trials)

System Organ Class Preferred Term	Nplate (n = 1078[a]) n (%)	Placebo/SOC (n = 138[b]) n (%)
Blood and lymphatic system disorders		
Thrombocytopenia	103 (9.6)	9 (6.5)
Idiopathic thrombocytopenic purpura	90 (8.3)	4 (2.9)
Anaemia	66 (6.1)	6 (4.3)
Gastrointestinal disorders		
Nausea	209 (19.4)	12 (8.7)
Diarrhoea	202 (18.7)	13 (9.4)
Vomiting	113 (10.5)	7 (5.1)
Gingival bleeding	107 (9.9)	13 (9.4)
Abdominal pain	98 (9.1)	7 (5.1)
Constipation	92 (8.5)	7 (5.1)
Mouth haemorrhage	83 (7.7)	6 (4.3)
Abdominal pain upper	71 (6.6)	9 (6.5)
Toothache	38 (3.5)	7 (5.1)
General disorders and administration site conditions		
Fatigue	251 (23.3)	29 (21.0)
Oedema peripheral	135 (12.5)	5 (3.6)
Pyrexia	127 (11.8)	11 (8.0)
Pain	86 (8.0)	5 (3.6)
Asthenia	78 (7.2)	3 (2.2)
Chest pain	55 (5.1)	5 (3.6)
Infections and infestations		
Nasopharyngitis	282 (26.2)	26 (18.8)
Upper respiratory tract infection	196 (18.2)	13 (9.4)
Influenza	98 (9.1)	3 (2.2)
Urinary tract infection	97 (9.0)	11 (8.0)
Sinusitis	77 (7.1)	3 (2.2)
Bronchitis	74 (6.9)	4 (2.9)
Injury, poisoning and procedural complications		
Contusion	243 (22.5)	29 (21.0)
Metabolism and nutrition disorders		
Hypokalaemia	34 (3.2)	7 (5.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	253 (23.5)	16 (11.6)
Back pain	170 (15.8)	10 (7.2)
Pain in extremity	168 (15.6)	10 (7.2)

System Organ Class Preferred Term	Nplate (n = 1078[a]) n (%)	Placebo/SOC (n = 138[b]) n (%)
Myalgia	121 (11.2)	2 (1.4)
Musculoskeletal pain	88 (8.2)	5 (3.6)
Muscle spasms	70 (6.5)	8 (5.8)
Nervous system disorders		
Headache	390 (36.2)	33 (23.9)
Dizziness	144 (13.4)	8 (5.8)
Paraesthesia	77 (7.1)	1 (0.7)
Psychiatric disorders		
Insomnia	114 (10.6)	13 (9.4)
Anxiety	56 (5.2)	7 (5.1)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	244 (22.6)	34 (24.6)
Cough	187 (17.3)	13 (9.4)
Oropharyngeal pain	131 (12.2)	6 (4.3)
Dyspnoea	76 (7.1)	7 (5.1)
Nasal congestion	62 (5.8)	3 (2.2)
Rhinorrhoea	54 (5.0)	4 (2.9)
Skin and subcutaneous tissue disorders		
Petechiae	200 (18.6)	27 (19.6)
Rash	122 (11.3)	10 (7.2)
Pruritus	87 (8.1)	7 (5.1)
Ecchymosis	68 (6.3)	11 (8.0)
Vascular disorders		
Haematoma	103 (9.6)	10 (7.2)
Hypertension	63 (5.8)	6 (4.3)

[a] population includes 104 paediatric patients; [b] population includes 5 paediatric patients

Serious adverse events/deaths/withdrawals/interventions from the two phase III placebo-controlled studies (Study 1 and 2)

Fourteen adult patients (17%) treated with Nplate (n = 84) experienced serious adverse events, two (2%) of whom had 3 serious adverse events assessed by the investigator as possibly related to treatment: bone marrow disorder determined to be increased reticulin, peripheral embolism, and peripheral ischemia. Eight (20%) patients treated with placebo (n = 41) experienced serious adverse events.

There were four fatal adverse events during the two placebo-controlled studies: 1 (1%) patient receiving Nplate and 3 (7%) placebo-treated patients); none of the deaths were considered

treatment-related. The Nplate-treated patient died following an intracranial haemorrhage that occurred after Nplate was discontinued in the presence of anti-platelet therapy. The fatal adverse events in the placebo-treated patients were (n (%)): cerebral haemorrhage (1 (2%)), pulmonary embolism (1 (2%)) and primary atypical pneumonia following hospitalisation for an intracranial bleed (1 (2%)).

Twenty-five patients discontinued treatment: 5 (6.0%) patients receiving Nplate and 20 (48.8%) placebo-treated patients. Three patients treated with Nplate discontinued treatment due to serious adverse events: B-cell lymphoma in a patient with pre-existing lymphadenopathy and several lymphoid aggregates in the bone marrow, bone marrow disorder determined to be increased reticulin, and intracranial haemorrhage after discontinuation of Nplate in the presence of anti-platelet therapy. One placebo-treated patient discontinued the study because of metastases to the liver.

Eighty three percent of patients in both Nplate and placebo groups had adverse events leading to intervention (e.g. alteration or discontinuation of study medication, other medications or therapies administered, hospitalisation). The most common adverse events leading to intervention in both the Nplate and placebo groups, respectively, were headache (29% vs. 27%), upper respiratory tract infection (13% vs. 10%), and arthralgia (12% vs. 7%).

Adverse drug reactions

Adults

Adverse drug reactions for Nplate are presented in Table 7 with frequencies derived from all thirteen clinical studies (Adult ITP Safety Set, n=1046). Among the adverse drug reactions in Table 7 are those where the subject incidence was ≥ 5% higher in the Nplate arm versus the placebo arm in the two Phase III placebo-controlled studies, (the majority of which were mild to moderate in severity), as well as those from across the entire adult ITP clinical program.

Table 7. Adverse Drug Reactions

MedDRA System Organ Class (SOC)	Adverse Reactions(Preferred Term [PT])	Frequency Category
Blood and lymphatic system disorders	Thrombocytopenia[a]	Common
	Thrombocytosis	Common
	Bone marrow reticulin fibrosis	Uncommon
Gastrointestinal disorders	Abdominal pain	Common
	Dyspepsia	Common
Immune system disorders	Hypersensitivity[#]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common
	Pain in extremity	Very common
	Myalgia	Very common
	Musculoskeletal pain[b]	Common
Nervous system disorders	Headache	Very common
	Dizziness	Very common
	Paraesthesia	Common
Psychiatric disorders	Insomnia	Very common
Skin and subcutaneous tissue disorders	Angioedema[#]	Uncommon
Vascular disorders	Haemorrhage	Common
	Erythromelalgia[#]	Uncommon

Frequency category is defined as follows: frequency of ≥ 1/10 is Very Common; frequency of ≥ 1/100 to < 1/10 is Common;frequency of ≥ 1/1000 to < 1/100 is Uncommon; frequency of < 1/1000 is Rare.

[a]*Thrombocytopenia events after cessation of romiplostim were identified by haematopoietic thrombocytopenia (SMQ) broad searchafter the last non-zero dose of romiplostim.*

[#]*Identified from post marketing experience and also observed in clinical trials (see Post-marketing experience)*

[b] *Data for only cases coded as Shoulder pain*

Adverse drug reactions from the two Phase III placebo-controlled studies (Study 1 and Study 2, (Nplate n=84, placebo n=41) that did not show a > 5% difference between the Nplate arm and the placebo arm included headache, which was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving Nplate and 32% of patients receiving placebo. Headache occurred at a higher incidence in splenectomised patients receiving Nplate (43%) compared with patients receiving placebo (33%) (Study 2, Nplate n=42, placebo n=21). In non-splenectomised patients, headaches occurred in 26% of patients receiving Nplate and 30% of patients receiving placebo (Study 1, Nplate n=42, placebo n=20). Headaches were usually mild or moderate and managed with non-narcotic analgesics.

Adverse drug reactions from the two Phase III placebo controlled studies with a 5% higher subject incidence in the Nplate arm (n=84) versus placebo arm (n=41) included arthralgia (26%

versus 20%),dizziness (17% versus 0%), insomnia (16% versus 7%), myalgia (14% versus 2%), pain in extremity (13% versus 5%), abdominal pain (11% versus 0%), shoulder pain (8% versus 0%), dyspepsia (7% versus 0%), and paraesthesia (6% versus 0%).

Less common adverse drug reactions observed from all thirteen clinical studies (Adult ITP Safety Set, n=1046) were recurrent thrombocytopenia after cessation of treatment with some patients developing thrombocytopenia of greater severity than was present prior to Nplate, increased bone marrow reticulin, and thrombocythemia (see section 4.4 Special warnings and precautions for use, Recurrence of thrombocytopenia after cessation of treatment, Increased bone marrow reticulin).

Long-term safety in adults

Information on the long-term safety of Nplate is derived from the 291 adult patients in the long-term extension study. The median duration of treatment in these patients was 78 weeks (range: 1 to 277 weeks), with a median weekly dose of 4 µg/kg.

Study duration-adjusted rates were calculated in order to account for the variable amounts of time that individual patients were enrolled on study. Study duration-adjusted adverse event incidence rates were expressed as the number of events per 100 patient-years on study. Two hundred and ninety-one adult patients reported 6933 adverse events while they were receiving Nplate for a study-duration adjustment event rate of 1106.5 events per 100 patient-years on study.

The most common adverse events (study duration-adjusted event rates) were headache (65.8 events per 100 patient-years), contusion (53.8 events per 100 patient-years), epistaxis (37.0 events per 100 patient-years), nasopharyngitis (29.7 events per 100 patient-years), arthralgia (24.9 events per 100 patient-years), and fatigue (39.6 events per 100 patient-years).

The serious adverse events expressed as study duration-adjusted event rates with >1% incidence rate were thrombocytopenia (4.9 events per 100 patient-years), ITP (2.6 events per 100 patient-years), congestive cardiac failure (2.1 events per 100 patient-years), and pneumonia (1.9 events per 100 patient-years).

Adult population with ITP duration up to 12 months

The safety profile of Nplate was similar across adult patients, regardless of ITP duration. Specifically in the integrated analysis of ITP ≤ 12 months duration (n=311), 277 adult patients with ITP ≤ 12 months duration and who received at least one dose of Nplate from among those patients in 9 ITP studies were included. In the integrated analysis, the following adverse reactions (at least 5% incidence and at least 5% more frequent with Nplate compared with placebo or standard of care) occurred in Nplate patients with ITP duration up to 12 months but

were not observed in those adult patients with ITP duration > 12 months: bronchitis (8.3%), sinusitis (5.4%), vomiting (7.2%).

Adverse events in paediatric studies

The Paediatric ITP Safety Set is comprised of patients from four paediatric clinical studies [20060195 (Phase I/II), 20030213 (Phase II open label, long term dose), 20080279 (Phase III), 20090340 (Phase II open label extension)].

The safety profile up to 24 weeks in the Nplate-treated patients in the Paediatric ITP Randomised Safety Set and the long-term safety in paediatrics were similar to that previously seen for Nplate.

Most adverse events were mild (grade 1) or moderate (grade 2) in severity. More paediatric patients receiving Nplate (24.5%) had serious adverse events compared with placebo (4.2%). The adverse event data for the placebo subjects reflected a shorter duration of exposure from participation in the randomised placebo-controlled studies 20060195 and 20080279. All subjects who enrolled in the longer duration extension studies received only Nplate. There were no fatal adverse events for subjects in either treatment group (see Table 8). There were no discontinuations (of study treatment or from study) due to AEs in the paediatric clinical studies.

Table 8. Adverse Events Reported in ≥ 5% incidence in Paediatric ITP Patients administered Nplate or Placebo/SOC by System Organ Class and Preferred Term (ITP Safety Set)

Preferred Term	Placebo (N = 24) n (%)	Nplate (N = 282) n (%)
Number of subjects reporting treatment-emergent adverse events	24 (100.0)	263 (93.3)
Headache	13 (54.2)	114 (40.4)
Epistaxis	11 (45.8)	111 (39.4)
Pyrexia	2 (8.3)	89 (31.6)
Nasopharyngitis	3 (12.5)	86 (30.5)
Vomiting	6 (25.0)	81 (28.7)
Contusion	8 (33.3)	80 (28.4)
Cough	3 (12.5)	78 (27.7)
Upper respiratory tract infection	6 (25.0)	75 (26.6)
Petechiae	7 (29.2)	69 (24.5)
Oropharyngeal pain	1 (4.2)	65 (23.0)
Nausea	7 (29.2)	60 (21.3)
Diarrhoea	3 (12.5)	60 (21.3)
Abdominal pain upper	1 (4.2)	58 (20.6)
Nasal congestion	3 (12.5)	44 (15.6)
Rhinorrhoea	3 (12.5)	43 (15.2)
Haematoma	2 (8.3)	43 (15.2)
Rash	2 (8.3)	40 (14.2)

Preferred Term	Placebo (N = 24) n (%)	Nplate (N = 282) n (%)
Abdominal pain	4 (16.7)	39 (13.8)
Gingival bleeding	4 (16.7)	38 (13.5)
Fatigue	5 (20.8)	36 (12.8)
Mouth haemorrhage	4 (16.7)	35 (12.4)
Pain in extremity	4 (16.7)	35 (12.4)
Arthralgia	4 (16.7)	34 (12.1)
Rhinitis	0 (0.0)	32 (11.3)
Ecchymosis	2 (8.3)	28 (9.9)
Pharyngitis	0 (0.0)	27 (9.6)
Dizziness	4 (16.7)	26 (9.2)
Skin abrasion	1 (4.2)	25 (8.9)
Viral infection	1 (4.2)	25 (8.9)
Laceration	7 (29.2)	23 (8.2)
Constipation	1 (4.2)	22 (7.8)
Influenza	0 (0.0)	22 (7.8)
Anaemia	1 (4.2)	21 (7.4)
Conjunctivitis	0 (0.0)	20 (7.1)
Ear infection	0 (0.0)	20 (7.1)
Ear pain	2 (8.3)	19 (6.7)
Pharyngitis streptococcal	0 (0.0)	19 (6.7)
Back pain	3 (12.5)	18 (6.4)
Fall	0 (0.0)	18 (6.4)
Decreased appetite	1 (4.2)	17 (6.0)
Pain	1 (4.2)	17 (6.0)
Myalgia	1 (4.2)	16 (5.7)
Gastroenteritis	0 (0.0)	16 (5.7)
Ligament sprain	0 (0.0)	16 (5.7)
Platelet count decreased	3 (12.5)	15 (5.3)
Seasonal allergy	0 (0.0)	15 (5.3)
Sinusitis	0 (0.0)	15 (5.3)
Thrombocytopenia	0 (0.0)	15 (5.3)
Scratch	3 (12.5)	14 (5.0)
Acne	2 (8.3)	14 (5.0)
Injection site pain	1 (4.2)	14 (5.0)
Head injury	2 (8.3)	13 (4.6)
Haemorrhage	2 (8.3)	12 (4.3)
Injection site bruising	3 (12.5)	11 (3.9)
Haematuria	2 (8.3)	8 (2.8)
Post procedural haemorrhage	2 (8.3)	7 (2.5)
Iron deficiency anaemia	2 (8.3)	6 (2.1)
Tooth socket haemorrhage	2 (8.3)	6 (2.1)
Pneumonia	2 (8.3)	5 (1.8)
Skin mass	2 (8.3)	5 (1.8)
Bone pain	2 (8.3)	4 (1.4)
Lip injury	2 (8.3)	3 (1.1)

Adverse reactions in paediatrics

The adverse drug reactions were determined by selecting treatment emergent adverse events (TEAEs) for subjects in either the Paediatric ITP Safety Set or Paediatric Randomised ITP Safety Set, who received at least one dose of Nplate and for which there was a ≥ 5% higher subject incidence in the Nplate group compared with the placebo group, as well as at least a 5% higher subject incidence in the Nplate-treated subjects (in either safety set). The majority of these adverse reactions were mild to moderate in severity (see Table 9).

Table 9. Adverse Drug Reactions

MedDRA System Organ Class (SOC)	Adverse Reactions	Frequency Category
Infections and Infestations	Nasopharyngitis Upper Respiratory Tract Infection Rhinitis Pharyngitis Conjunctivitis Ear infection Gastroenteritis Sinusitis	Very Common Very Common Very Common Common Common Common Common Common
Respiratory, Thoracic and MediastinalDisorders	Cough Oropharyngeal Pain	Very Common Very Common
Gastrointestinal Disorders	Abdominal Pain Upper Diarrhoea	Very Common Very Common
Skin and Subcutaneous Tissue Disorders	Rash Purpura Urticaria	Very Common Common Common
General Disorders and Administration SiteConditions	Pyrexia Peripheral Swelling	Very Common Common
Injury, Poisoning and ProceduralComplications	Contusion	Very Common
Frequency category is defined as follows: frequency of ≥ 1/10 is Very Common; frequency of ≥ 1/100 to < 1/10 is Common; frequency of ≥ 1/1000 to < 1/100 is Uncommon; frequency of < 1/1000 is Rare.		

The adverse drug reaction of thrombocytosis occurred uncommonly, with a subject incidence in the Paediatric ITP Safety Set of 1 (0.4 %). Subject incidence was 1 (0.4 %) for either grade ≥3 or serious thrombocytosis.

In paediatric patients of age ≥ 1 year receiving Nplate for ITP, adverse drug reactions with a subject incidence of ≥ 10 % in the overall Paediatric ITP Randomised Safety Set (Study 5 and

Study 4) were contusion (41 %), upper respiratory tract infection (31 %), and oropharyngeal pain (25 %), pyrexia (24%), diarrhoea (20%), rash (15%) and abdominal pain upper (14%).

Nasopharyngitis, upper respiratory tract infection, rhinitis, pharyngitis, conjunctivitis, ear infection, gastroenteritis, sinusitis, cough, oropharyngeal pain, abdominal pain upper, diarrhoea, rash, purpura, urticaria, pyrexia, peripheral swelling, contusion were additional adverse reactions from paediatric studies compared to those seen in adult studies. The adverse reaction thrombocytosis in adult studies occurred commonly (Common, ≥ 1/100 to < 1/10), compared to at a lower subject incidence in paediatric studies (Uncommon, ≥1/1000 to < 1/100).

Analysis of reported bleeding events

Adults

In the two Phase III placebo-controlled studies (Study 1 and 2) an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (≥ grade 3) bleeding events occurred at platelet counts < 30 x 10^9/L. All bleeding events > grade 2 occurred at platelet counts < 50 x 10^9/L.

The incidence of bleeding events in the two Phase III adult placebo-controlled studies (Study 1 and 2) is shown in Table 10. Nine patients reported a bleeding event that was considered serious (5 (6%) Nplate, 4 (10%) placebo). Bleeding events that were grade 2 or higher were reported by 15% of patients treated with Nplate and 34% of patients treated with placebo (see Table 10).

Table 10. Incidence of Bleeding events in Study 1 and 2 - Phase III placebo-controlled studies conducted in adults

Bleeding events	**Nplate (n = 84)**	**Placebo(n = 41)**
Serious[a]	5 (6%)	4 (10%)
Grade 2 or higher[b]	13 (15%)	14 (34%)

[a] met protocol-defined criteria for seriousness (includes any event that is fatal, life-threatening, requires hospitalisation or prolongation of hospitalisation, causes persistent or significant disability/incapacity, congenital anomaly/birth defect and any other significant hazard).

[b] Grade 1 – mild; Grade 2 – moderate; Grade 3 – severe; Grade 4 – life-threatening; Grade 5 – fatal

For the Phase III ITP long-term safety set, the study duration-adjusted event rate of grade 2 or higher bleeding events was 98 per 100 patient-years for patients treated with Nplate and 132 per 100 patient-years for placebo-treated patients.

These trends in bleeding event rates were observed in the context of a greater reduction of concomitant ITP medications among patients receiving Nplate relative to placebo. In addition,

there was a higher incidence of rescue medication use among patients receiving placebo (see section 5.1 Pharmacodynamic properties, Use of rescue therapies).

In study 4 (open-label study), the duration-adjusted incidence of grade 2 or higher bleeding events was 24 per 100 patient-years in patients treated with Nplate and 36 per 100 patient-years in patients receiving the standard of care.

Paediatrics

In the Phase III paediatric study, the mean (SD) number of composite bleeding episodes was 1.9 (4.2) for the Nplate arm and 4.0 (6.9) for the placebo arm. The subject incidence of rescue medication use, a secondary objective, was not statistically significant (see section 5.1 Clinical trials).

In Study 5, the composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinically significant bleeding event during weeks 2 through 25 of the treatment period. A clinically significant bleeding event was defined as a Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade ≥ 2 bleeding event. The mean (SD) number of composite bleeding episodes (clinical grade ≥ 2) was 1.9 (4.2) for the Nplate arm and 4.0 (6.9) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the Nplate arm and 0.5 (0, 4.5) in the placebo arm. The overall duration-adjusted rate per 100 subject-years was 8.1 in the Nplate arm and 18.4 in the placebo arm. In an ad hoc analysis, the duration-adjusted rate (per 100 patient-weeks) of these episodes was lower with Nplate than placebo (8.1 vs 18.4; treatment difference -10.3, 95% CI - 14.7, -5.9).

Immunogenicity

Romiplostim has no amino acid sequence homology to endogenous thrombopoietin (eTPO). Therefore, any anti-product antibodies formed are unlikely to cross react with eTPO.

Clinical trial patients were screened for immunogenicity to Nplate using an immunoassay capable of detecting both high and low affinity binding antibodies that bind to romiplostim and cross-react with eTPO. The samples that tested positive for binding antibodies were further evaluated for neutralising capacity.

In a pooled analysis of adult ITP subjects treated with Nplate the incidence of pre-existing antibodies to romiplostim was 3.7% (35/958), and the incidence of binding antibody development during Nplate treatment was 6.2% (60/961). The incidence of pre-existing antibodies to eTPO was 3.2% (31/956) and the incidence of binding antibody development to eTPO during Nplate treatment was 3.4% (33/960). Of the adult patients with positive binding antibodies that developed to either romiplostim or TPO, 4 patients had neutralising activity to romiplostim, but these antibodies did not cross react with endogenous TPO.

As with all therapeutic proteins, there is a potential for immunogenicity. If formation of neutralising antibodies is suspected, contact Amgen to perform assays for antibodies.

If severe thrombocytopenia develops during Nplate treatment, assess patients for the formation of neutralising antibodies.

In a pooled analysis of paediatric patients ITP patients treated with Nplate, the incidence of binding antibodies to romiplostim at any time was 9.6% (27/282). Of the 27 paediatric patients, 2 had pre-existing binding non-neutralising romiplostim antibodies at baseline. Additionally, 2.8% (8/282) developed neutralising antibodies to romiplostim during treatment. A total of 3.9% (11/282) paediatric patients had binding antibodies to TPO at any time during Nplate treatment. Of these 11 paediatric patients, 2 had pre-existing binding non-neutralising antibodies to TPO and none had neutralising activity to TPO. One patient (0.35%) had a weakly positive post-baseline result for neutralising antibodies against TPO while on study (consistently negative for anti-romiplostim antibodies) with a negative result at baseline. The patient showed a transient antibody response for neutralising antibodies against TPO, with a negative result at the patient's last timepoint tested within the study period.

In the post marketing registry study, a total of 2.2% (4/184) adult patients developed binding, non-neutralising antibody against TPO. The incidence of binding antibody post treatment was 3.8% (7/184) to romiplostim, of which 0.5 % (1/184) was positive for neutralising antibodies to romiplostim. In paediatric patients, the incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralising antibodies to romiplostim. There were no antibodies detected to TPO.

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

<u>Post-marketing experience</u>

Cases of erythromelalgia have been reported.

Cases of hypersensitivity reactions including angioedema have been reported. Patients also experienced symptoms consistent with anaphylaxis.

Cases of acute myocardial infarction have been reported.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/ thromboembolic complications. If the platelet counts are excessively increased, treatment with Nplate should be discontinued and platelet counts should be monitored (see section 4.4 Special warnings and precautions for use, Recurrence of thrombocytopenia after cessation of treatment, Thrombotic/Thromboembolic complications and Medication errors).

Reinitiate treatment with Nplate in accordance with Dose and method of administration.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical group: antihaemorrhagics, other systemic haemostatics; ATC code: B02BX04

Mechanism of action

Romiplostim increases platelet production through binding and activation of the thrombopoietin receptor, a mechanism analogous to endogenous thrombopoietin (eTPO). The TPO receptor is predominately expressed on cells of the myeloid lineage such as megakaryocyte progenitor cells, megakaryocytes and platelets.

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet count. The peak platelet counts in immune (idiopathic) thrombocytopenic purpura (ITP) patients who received a single subcutaneous dose of 1-10 µg/kg Nplate were 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 week period; the response was variable among patients. The platelet counts of ITP patients who received doses of 1 or 3 µg/kg Nplate at weekly intervals for 6 weeks were within the range of 50 to 450 x 10^9/L for most patients, but the response was variable. Individual dose adjustment of Nplate is recommended, and the dose adjustment should be based on the observed platelet count (see section 4.2 Dose and method of administration).

Clinical trials

Adults

The safety and efficacy of Nplate in adults was evaluated in two Phase III, randomised, placebo-controlled, double-blind studies in adults with chronic ITP (Study 1 and Study 2) and an open-label single-arm study (Study 3).

Study 1 and Study 2 were conducted in adults with ITP who had completed at least one treatment and had a platelet count of ≤ 30 x 10^9/L prior to study entry; they are representative of the entire spectrum of such ITP patients.

Study 1 (20030212)

Study 1 (20030212) evaluated patients who had not undergone a splenectomy and had an inadequate response or were intolerant to prior ITP therapies. Patients had been diagnosed with ITP for a median of 2.1 years (range 0.1 to 31.6) at the time of study entry. Patients had a median of 3 (range 1 to 7) treatments for ITP prior to study entry and a median platelet count of 19 x 10^9/L. Study 2 (20030105) evaluated patients who had undergone a splenectomy and continued to have thrombocytopenia. Patients had been diagnosed with ITP for median of 8 years (range 0.6 to 44.8) at the time of study entry. In addition to a splenectomy, patients had received a median of 6 (range 3 to 10) treatments for ITP prior to study entry. Their median platelet count was 14 x 10^9/L at study entry.

With exception of splenectomy status, study design was the same for both studies. Patients (≥ 18 years) were randomised 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. A durable platelet response was defined as a weekly platelet count ≥ 50 x 10^9/L for at least 6 weeks during weeks 18 through 25 in the absence of rescue therapy at any time during the treatment period. In the placebo-controlled studies, the most frequently used weekly dose for splenectomised patients was between 2 and 7 µg/kg (25th-75th percentile respectively; median 3 µg/kg). For non-splenectomised patients, it was between 1 and 3 µg/kg (25th-75th percentile respectively; median 2 µg/kg).

A significantly higher proportion of patients receiving Nplate achieved a durable platelet response compared to patients receiving placebo in both studies: Study 1, 61% versus 5% and Study 2, 38% versus 0%, respectively (see Table 11). Treatment with Nplate provided significant improvements compared to placebo in both clinical studies for all efficacy endpoints for all patients randomised to the studies based on an intention to treat analysis (see Table 11).

Table 11. Summary of efficacy results from placebo-controlled studies in Adults

	Study 1 Non-splenectomised Patients		Study 2 Splenectomised Patients		Combined Studies 1 & 2	
	Nplate (n = 41)	Placebo (n = 21)	Nplate (n = 42)	Placebo (n = 21)	Nplate (n = 83)	Placebo (n = 42)
Primary Endpoint						
No. (%) Patients with Durable Platelet Response[a]	25 (61%)	1 (5%)	16 (38%)	0 (0%)	41 (50%)	1 (2%)
(95% CI)	(45%, 76%)	(0%, 24%)	(24%, 54%)	(0%, 16%)	(38%, 61%)	(0%, 13%)
p-value	<0.0001		0.0013		<0.0001	
Key Secondary Endpoints						
No. (%) Patients with Overall Platelet Response[b]	36 (88%)	3 (14%)	33 (79%)	0 (0%)	69 (83%)	3 (7%)
(95% CI)	(74%, 96%)	(3%, 36%)	(63%, 90%)	(0%, 16%)	(73%, 91%)	(2%, 20%)
p-value	<0.0001		<0.0001		<0.0001	
Mean No. Weeks with Platelet Response[c]	15	1	12	0	14	1
(SD)	7.5	3.5	7.9	0.5	7.8	2.5
p-value	<0.0001		<0.0001		<0.0001	
No. (%) Patients Requiring Rescue Therapies[d]	7 (17%)	13 (62%)	11 (26%)	12 (57%)	18 (22%)	25 (60%)
(95% CI)	(7%, 32%)	(38%, 82%)	(14%, 42%)	(34%, 78%)	(13%, 32%)	(43%, 74%)
p-value	0.0004		0.0175		<0.0001	
No. (%) Patients with Durable Platelet Response with Stable Dose[e]	21 (51%)	0 (0%)	13 (31%)	0 (0%)	34 (41%)	0 (0%)
(95% CI)	(35%, 67%)	(0%, 16%)	(18%, 47%)	(0%, 16%)	(30%, 52%)	(0%, 8%)
p-value	0.0001		0.0046		<0.0001	

[a] Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for study weeks18-25 in the absence of rescue therapy any time during the treatment period.

[b] Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 4 or more times during study weeks 2-25, but withoutdurable platelet response. Patient may not have a weekly response within 8 weeks after receiving rescue therapy.

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

[d] Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue therapy were not considered for durable platelet response. Rescue therapies allowed in the study were normal human immunoglobulin (IVIG), platelet transfusions, anti-RhD immunoglobulin, and corticosteroids.

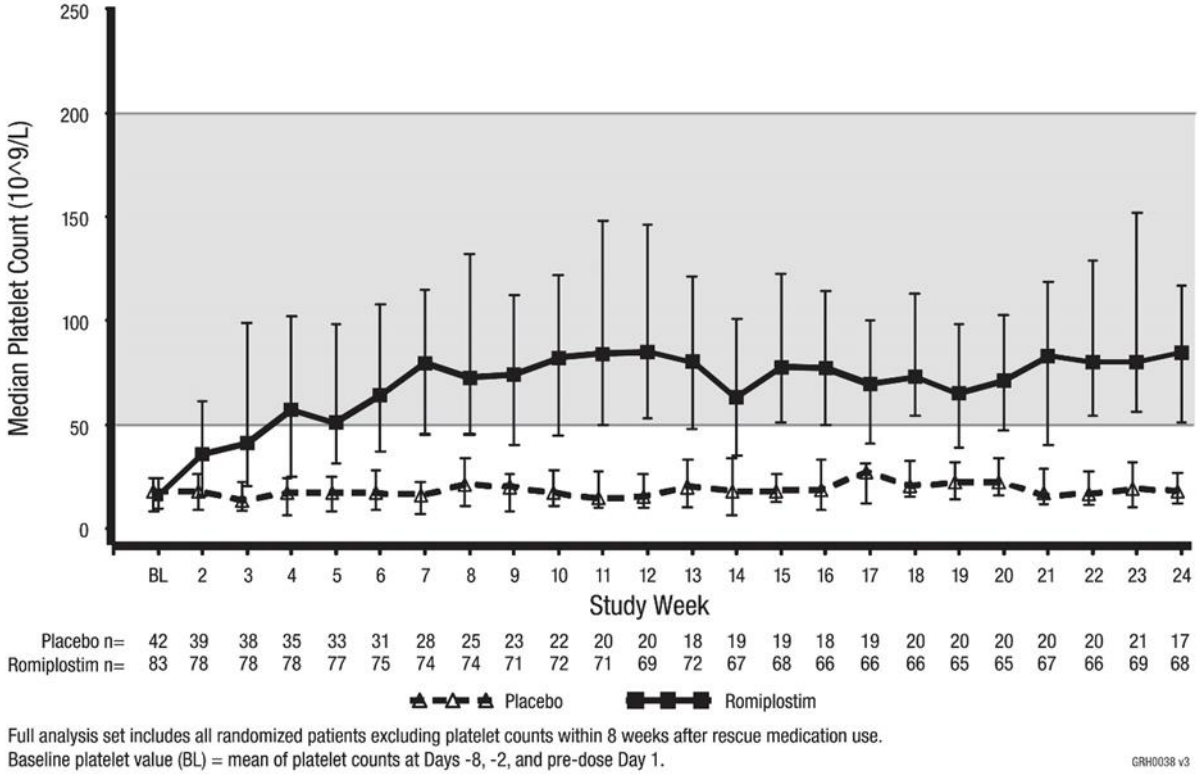
[e] Stable dose was defined as dose maintained within ± 1 µg/kg during the last 8 weeks of treatment.

In both Study 1 and Study 2, 30% of patients treated with Nplate achieved a platelet count above 50 x 10^9/L by week 2, 54% by week 4, and 50% to 70% of patients maintained platelet counts ≥ 50 x 10^9/L for the remainder of the 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 1 shows the median weekly platelet counts over the 6 months of treatment in the treatment period in the phase III studies.

Figure 1. Median weekly platelet counts in Adult phase III studies

(Vertical lines represent the first and third quartiles around the median)



Full analysis set 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.

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Following discontinuation of Nplate during both studies, 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 open-label extension study.

Results of studies in adult patients with newly diagnosed and persistent ITP

Study 3 (20080435)

This was a single-arm, open label study in adult patients who had an insufficient response (platelet count ≤ 30 x 10^9/L) to first line therapy. The study enrolled 75 patients of whom the median age was 39 years (range 19 to 85) and 59% were female. The median time from ITP diagnosis to study enrolment was 2.2 months (range 0.1 to 6.6). Sixty percent of patients had ITP duration < 3 months and 40% had ITP duration ≥ 3 months. The median platelet count at screening was 20 x 10^9/L. Prior ITP treatments included corticosteroids, immunoglobulins and anti-D immunoglobulins. Patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the studies. Rescue therapies (i.e. corticosteroids, IVIG, platelet transfusions, anti-D immunoglobulin, dapsone, danazol, and azathioprine) were permitted.

Patients received single weekly SC injections on Nplate over a 12-month treatment period, with individual dose adjustments to maintain platelet counts (50 x 10^9/L to 200 x 10^9/L). During the study the median weekly Nplate dose was 3 µg/kg (25th 75th percentile: 2-4 µg/kg).

Of the 75 patients enrolled is Study 3, 70 (93%) had a platelet response ≥ 50 x 10^9/L during the 12-month treatment period. The mean number of months with platelet response during the 12-month treatment period was 9.2 (95% CI: 8.3, 10.1) months; the median was 11 (95% CI: 10, 11) months. The Kaplan Meier estimate of the median time to first platelet response was 2.1 weeks (95% CI: 1.1, 3.0). Twenty-four (32%) patients had sustained treatment-free remission as defined by maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months in the absence of Nplate and any medication for ITP (concomitant or rescue); the median time to onset of maintaining every platelet count ≥ 50 x 10^9/L for at least 6 months was 27 weeks (range 6 to 57).

Use of Nplate in non-splenectomised ITP patients compared with medical standard of care

Study 4 (20060131)

Study 4 was an open-label study evaluating the safety and efficacy of Nplate compared with medical standard of care (SOC) treatment in non-splenectomised adult patients (aged ≥ 18 years) with ITP and platelet counts < 50 x 10^9/L, who received at least one prior standard therapy for ITP. Patients had been diagnosed with ITP for a median of 2 years (range 0.01 to 44.2) at the time of study entry. Patients had a median platelet count at enrolment of 29 x 10^9/L. Medical SOC treatments were selected and prescribed by the investigator according to standard institution practices or therapeutic guidelines.

Patients were randomised in a 2:1 ratio to receive a starting dose of Nplate 3 µg/kg or SOC. Nplate was administered by single weekly SC injections for 52 weeks. Doses were adjusted throughout the study within a range of 1 to 10 µg/kg in order to maintain platelet counts (50 to 200 x 10^9/L). Of the 157 patients randomised to receive Nplate, the median (range) duration of exposure was 52.0 weeks (2 to 53). The most frequently used weekly dose was between 3 and 5 µg/kg (25^{th}-75^{th} percentile respectively; median 3 µg/kg).

For both co-primary endpoints, the Nplate group showed significantly greater improvement (i.e., lower rate of splenectomy and lower rates of treatment failure) compared to patients assigned to receive SOC. As shown in Table 12, the odds of undergoing a splenectomy is significantly lower in the Nplate group than the SOC group, with an odds ratio (Nplate vs. SOC) of 0.17 (95% CI: 0.15, 0.61).

Table 12. Summary of efficacy results from open-label study 4 (20060131)

	Study 4 Non-splenectomised Patients	
	Nplate (n = 157)	**Standard of Care (SOC) (n = 77)**
Incidence rate of Splenectomy[a]	14 (8.9%)	28 (36.4%)
(95% CI)	(5%, 14.5%)	(25.7%, 48.1%)
p-value[b]	<0.0001	
Incidence of treatment failure[c]	18 (11.5%)	23 (29.9%)
(95% CI)	(6.9%, 17.5%)	(20%, 41.4%)
p-value[b]	0.0005	

[a] Patients who discontinued study during treatment period prior to reporting a splenectomy were considered ashaving a splenectomy.

[b] From stratified Cochran-Mantel-Haenszel (CMH) controlling for the geographic region of investigational sites(North America, European Union, and Australia).

[c] Patients who discontinued study during treatment period prior to observing a treatment failure were consideredas having had a treatment failure. Treatment failure: platelet count ≤ 20 x 10^9/L for 4 consecutive weeks at the highest recommended dose and schedule, or major bleeding event, or change in therapy due to intolerable sideeffects or bleeding symptoms.

Paediatrics

The safety and efficacy of Nplate in paediatric patients aged 1 year and older with ITP were evaluated in two randomised, placebo-controlled, double-blind studies (Study 5 and Study 6).

Study 5 (20080279) was a Phase III study with 24 weeks of Nplate treatment and Study 6 (20060195) was a Phase I/II study with 12 weeks of Nplate treatment (up to 16 weeks for eligible responders who entered a 4-week pharmacokinetic assessment period).

Both studies enrolled paediatric patients (≥ 1 year to < 18 years of age) with thrombocytopenia (defined by a mean of two platelet counts ≤ 30 x 10^9/L with neither count > 35 x 10^9/L in both studies) with ITP, regardless of splenectomy status.

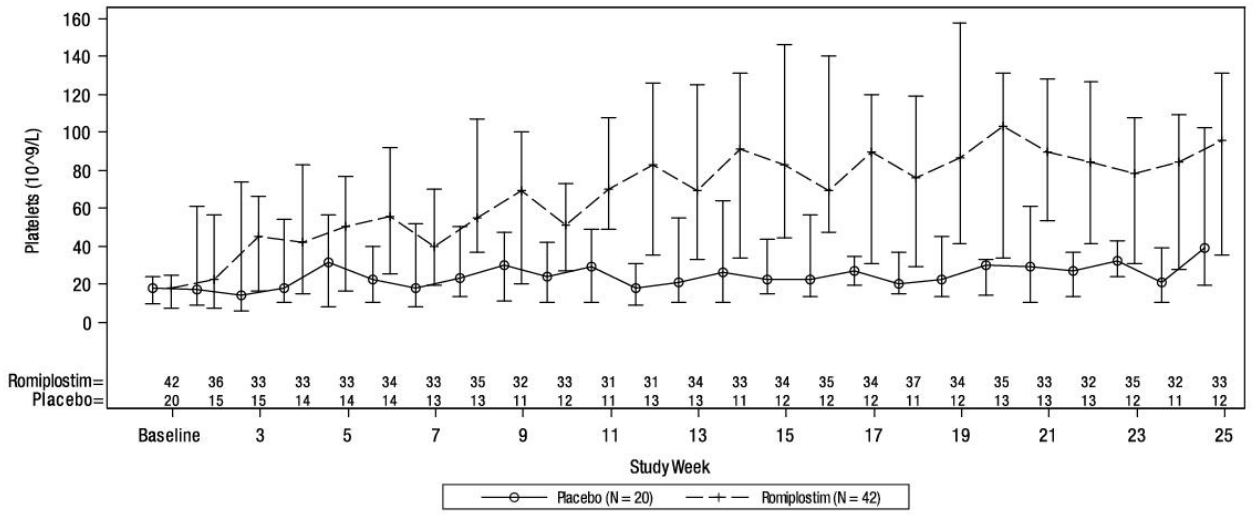
Study 5 (20080279)

Sixty-two patients were randomised in a 2:1 ratio to receive Nplate (n = 42) or placebo (n = 20) and stratified into 1 of 3 age cohorts. In the pivotal Phase III placebo-controlled study, the starting dose of Nplate was 1 µg/kg and weekly dose increments continued in increments of 1 µg/kg to a maximum dose of 10 µg/kg in an attempt to reach the target platelet count > 50 x 10^9 µg/kg/L. The most frequently used weekly dose was between 3 – 10 µg /kg and the maximum allowed dose on study was 10 µg /kg (25th - 75th percentile respectively; median 5.5 µg/kg). Patients received single subcutaneous weekly injections for 24 weeks.

The primary endpoint was the incidence of durable response, defined as achieving at least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of treatment. Overall, a significant greater proportion of patients in the Nplate arm achieved the primary endpoint

compared with patients in the placebo arm (p = 0.0018). A total of 22 patients (52%) had durable platelet response in the Nplate arm compared with 2 (10%) in the placebo arm: ≥ 1 to < 6 years 38% vs 25%; ≥ 6 to < 12 years 56% vs 11%; ≥ 12 to < 18 years 56% vs 0 (see Table 13).

Figure 2. Median weekly platelet counts in Paediatric phase III studies



Vertical lines represent the first and third quartiles around the median.
Platelet counts measured within 4 weeks following a rescue medication use or after splenectomy were excluded.

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Study 6 (20060195)

Twenty-two paediatric patients were randomised in a 3:1 ratio to receive romiplostim (n = 17) or placebo (n = 5). Doses were increased in increments of 2 µg/kg every 2 weeks and the target platelet count was ≥ 50 x 10^9/L. Treatment with Nplate resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0008). None of the patients in the placebo arm achieved either endpoint (see Table 13). No statistical test was performed for the number of composite bleeding episodes endpoint as the statistical testing for the incidence of rescue medication use was not significant.

Table 13: Summary of efficacy results from placebo-controlled studies in Paediatrics

Study 5		
	Nplate (n = 42)	Placebo (n = 20)
No. (%) Patients with Durable Platelet Response [a]	22 (52%)	2 (10%)
≥ 1 to < 6 years	38%	25%
≥ 6 to < 12 years	56%	11%
≥ 12 to < 18 years	56%	0%
Mean SD number of composite bleeding episodes (clinical grade ≥ 2) [a]	1.9 (4.2)	4.9 (6.9)
Median (Q1, Q3) number of bleeding events	0 (0.20)	0 (0, 4.5)

[a] Composite bleeding is defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinically significant bleeding event during weeks 2 through 25 of the treatment period.

Study 6		
	Nplate (n = 17)	Placebo (n = 5)
Platelet count of ≥ 50 x 10^9/L for 2 consecutive weeks during treatment period	15 (88.2 %)	0 (0%)
(95% CI)	(63.6%, 98.5%)	0%
Platelet count of ≥ 20 x 10^9/L for 2 consecutive weeks during treatment period	15 (88.2 %)	0 (0%)
(95% CI)	(63.6%, 98.5%)	0%

Reduction in permitted concurrent ITP medical therapies

Adults

In both placebo-controlled, double-blind studies, patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the study (i.e. corticosteroids, danazol and/or azathioprine). Twenty-one non-splenectomised and 18 splenectomised patients received on-study ITP medical treatments (primarily corticosteroids) at the start of study. All splenectomised patients who were receiving Nplate were able to reduce the dose by more than 25% or discontinue the concurrent ITP medical therapies by the end of the treatment period compared to 17% of the placebo-treated patients. Seventy three percent of non-splenectomised patients receiving Nplate were able to reduce the dose by more than 25% or discontinue concurrent ITP medical therapies by the end of the study compared to 50% of placebo-treated patients.

Paediatrics

In the integrated analysis, the prevalence of concurrent ITP therapy use was 42.6% (120 of 282 patients) and the incidence of rescue medication use was 33.7% (95 of 282) at any time during

treatment. There was a reduction in concomitant medication use over time. The prevalence of concurrent ITP therapy use was 34.0% from months 1 to 6, 23.2% from months 7 to 12, 18.1% in year 2, 17.6% in year 3, 12.1% in year 4, 5.6% in year 5, and 0% from year 6 through year 10 (with the exception of the use of concomitant medications reported in 1 subject [12.5%] in year 7).

The incidence of rescue medication use was 33.7% (95 of 282 paediatric patients) at any time during treatment. There was a reduction in rescue medication over time. The incidence of rescue medication use was 25.5% from months 1 to 6, 15.4% from months 7 to 12, 11.4% in year 2, 11.8% in year 3, and 6.1% in year 4. There was no reported rescue medication use in years 5 through year 10.

Use of rescue therapies

Adults

Rescue therapies (i.e. corticosteroids, normal immunoglobulin (IVIG), platelet transfusions, anti-D Rho immunoglobulin) were permitted in both placebo-controlled, double-blind studies for bleeding, wet purpura, or if the patient was at immediate risk of bleeding. The total incidence of rescue therapy use was considerably higher for placebo-treated patients than for Nplate treated patients (see Table 11).

In both placebo-controlled, double-blind studies, patients already receiving ITP medical therapies at a constant dosing schedule were allowed to continue receiving these medical treatments throughout the study (i.e. corticosteroids, danazol and/or azathioprine). Twenty-one non-splenectomised and 18 splenectomised patients received on-study ITP medical treatments (primarily corticosteroids) at the start of study. All splenectomised patients who were receiving Nplate were able to reduce the dose by more than 25% or discontinue the concurrent ITP medical therapies by the end of the treatment period compared to 17% of the placebo-treated patients. Seventy three percent of non-splenectomised patients receiving Nplate were able to reduce the dose by more than 25% or discontinue concurrent ITP medical therapies by the end of the study compared to 50% of placebo-treated patients.

Paediatrics

The incidence of rescue medication use was 32.6% (73 of 224 paediatric patients) at any time during treatment. There was a trend towards a reduction in rescue medication over time.

Long term extension study

Adults

Adult patients who had completed a prior Nplate study (including the Phase III studies) were allowed to enrol in a long-term open-label extension study. Subjects were enrolled after completing a previous romiplostim ITP study. Following subsequent amendments there was no

requirement for subjects to wait until platelet counts had fallen to < 50 x 10^9/L, and to wash out certain ITP treatments prior to entering the study.

Patients in the long-term extension continued with weekly dosing and individual dose adjustments of Nplate based on platelet counts. Patients who had received placebo in the placebo-controlled studies received an initial dose of 1 µg/kg Nplate in the extension study. Patients who were treated with Nplate in the placebo-controlled studies were re-initiated at their previous dose of Nplate, if the Nplate-free period was < 24 weeks; if > 24 weeks, patients received an initial dose of 1 µg/kg Nplate. The majority of patients treated with Nplate responded quickly, reaching a median count of 50 x 10^9/L after receiving 1 to 3 doses of Nplate. These platelet counts were maintained within the therapeutic range of 50 to 200 x 10^9/L throughout the remainder of the study.

Results from an integrated analysis of patients from the placebo-controlled studies who continued into the extension study support the long-term use of Nplate (median duration 78 weeks, with 292 adult patients treated for up to 277 weeks).

After the initial dose adjustment period, the majority (> 75%) of adult patients were able to maintain their dose within 2 µg/kg, suggesting maintenance of clinical effect over time in the absence of significant Nplate dosage increases. The overall incidence of rescue medication use in adult patients was 33.3%. Approximately 13% (37/292) of adult patients entered this study on concurrent ITP therapy. Twenty (54.1%) of these patients discontinued concurrent ITP therapy by the end of the study. Patients who had bone marrow biopsies (n = 38) showed no evidence of type I collagen. However, trichrome staining for type I collagen was inconsistently performed.

Data from patients previously treated with Nplate in one of the placebo-controlled studies confirm the ability of Nplate to sustain a response over an extended period of time in the majority of patients. In addition, these data demonstrate the ability of Nplate to increase platelet counts in patients from the studies who previously received placebo. Former placebo patients who received Nplate in the extension study showed a pattern of platelet count increases similar to patients who received Nplate in the pivotal studies.

Due to the heterogeneity of the population with regard to inclusion criteria, disease baseline characteristics, treatment history, concurrent medication, Nplate dose received and length of treatment included in this study, data on the long-term efficacy and safety of Nplate should be interpreted with caution.

Paediatrics

Study 7 (20030213)

Study 7, conducted in 20 paediatric patients, was an extension of the Phase I/II study (Study 6). Paediatric patients in Study 7 were administered Nplate once weekly.

Patients who had received placebo in the placebo-controlled studies received an initial dose of 1 µg/kg Nplate in the extension study. Patients who were treated with Nplate in the placebo-controlled studies were re-initiated at their previous dose of Nplate.

Platelet response (≥ 50 x 10^9/L at any time during the study) was achieved in 100.0% of the paediatric patients (95% CI: 83.2%, 100.0%). A platelet count of ≥ 100 x 10^9/L was reached in 90.0% of paediatric patients and a peak platelet count of ≥ 150 x 10^9/L was reached in 85.0% of paediatric patients. The overall incidence of rescue medication use in study 6 was 20.0% (4 paediatric patients).

Study 8 (20090340)

Study 8 (20090340), conducted in 65 paediatric patients, was an extension of clinical studies 20030213 (Phase II open label) and 20080279 (Phase III). Sixty-five paediatric patients received at least one dose of Nplate and one subject withdrew from the study before the first dose of Nplate. Nplate was administered subcutaneously on a weekly basis with a maximum permitted dose of 10 µg/kg. Across the study, the overall subject incidence of platelet response (1 or more platelet count ≥ 50 x 10^9L in the absence of rescue medication) was 93.8% (61 of 65 patients). The subject incidence of platelet response was similar across age groups and similar between subjects coming from either of the previous studies.

Study 9 (20101221)

Study 9 (20101221), conducted in 203 paediatric patients, was a Phase III single arm open label multicentre study in patients with ITP diagnosed for at least 6 months and who received at least one prior ITP therapy (excluding Nplate) or were ineligible for other ITP therapies. Two hundred and four patients were enrolled in the study across three age groups. Of these, 203 patients received at least one dose of Nplate and 1 patient did not receive Nplate. Nplate was administered subcutaneously, on a weekly basis, with a starting dose of 1 µg/kg in increments to a maximum dose of 10 µg/kg, to attain a target platelet count between 50 x 10^9/L and ≤ 200 x 10^9/L.

The incidence of patients who had at least one platelet response from week 2 to end of study was 88.2 % (179 of 203 patients) overall and was similar across all age groups. Analysis of platelet response rate over time showed that overall percentage of patients with a platelet

response at week 2 was 23 %. The total response rate increased over time on overall study and across all age groups.

Open label study evaluating changes in bone marrow reticulin and collagen

Adults

An open-label trial prospectively evaluated bone marrows for reticulin formation and collagen fibrosis in adult patients with ITP receiving Nplate treatment. The modified Bauermeister grading scale was used for both assessments. Patients were administered Nplate by subcutaneous injection once weekly for up to 3 years. Based on cohort assignment at time of study enrolment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1), year 2 (cohort 2) or year 3 (cohort 3) in comparison to the baseline bone marrow at start of study. From the total of 169 patients enrolled in the 3 cohorts, 132 (78.1%) patients were evaluable for bone marrow collagen fibrosis and 131 (77.5%) patients were evaluable for bone marrow reticulin formation. In total, 1.5% (2 of 132) of patients with an evaluable bone marrow trichome stain result developed collagen. There was no detectable collagen in the one patient who underwent repeat testing 12 weeks after discontinuation of Nplate.

Progression of reticulin fibre formation of modified Bauermeister grade greater than or equal to 2 grades or more change or an increase to Grade 4 collagen was reported in 6.9% (9/131) of patients: 0/34 subjects in Cohort 1 (at 1 year), 2/39 (5.1%) subjects in Cohort 2 (at 2 years) and 7/58 (12.1%) subjects in Cohort 3 (at 3 years).

Among those subjects who had an increased modified Bauermeister grade to grade 3 or grade 4 and underwent follow-up bone marrow biopsy in the study, increases in reticulin grade were reversible after discontinuation of romiplostim. Reticulin was not associated with adverse clinical sequelae.

Paediatrics

An open label clinical trial evaluated the incidence of changes in bone marrow findings and increased reticulin at year 1 or year 2 following exposure to Nplate. The modified Bauermeister grading scale was used for both assessments. Patients were administered Nplate by subcutaneous injection once weekly for up to 3 years.

Sixty-six patients were enrolled in the study and of these patients, 30 patients were in cohort 1 (bone marrow samples were taken at baseline and year 1) and 36 patients were in cohort 2 (bone marrow samples taken at baseline and year 2).

No patients demonstrated any bone marrow abnormalities that were not consistent with an underlying diagnosis of ITP at baseline or during treatment. The Bauermeister scores of patients were below 1 at either baseline or during treatment, no patient met the primary

endpoints for the development of collagen or increased bone marrow. At the end of the clinical study, there were no patients that had repeat follow-up bone marrow biopsy, as this was only performed on patients that are withdrawn from the study due to the presence of collagen or change to grade 3 reticulin.

5.2 Pharmacokinetic properties

Distribution

The pharmacokinetics of romiplostim involves target-mediated disposition through binding to the TPO receptors on the platelets and megakaryocytes. This results in non-linear volume of distribution and clearance.

The serum concentration of romiplostim administered at pharmacologically active doses (< 3 µg/kg) was not measurable in most samples collected from healthy volunteers and

patients with ITP, despite the use of a very specific and sensitive ELISA with a lower limit of quantification of 18 pg/mL.

In patients with ITP who received chronic weekly treatment of Nplate subcutaneously (median duration of treatment 39 weeks, with up to 84 weeks for 100 patients), the pharmacokinetics of romiplostim over the dose range of 3 to 15 µg/kg indicated that peak serum concentrations were observed about 7 to 50 hours post-dose (median: 14 hours). The half-life values ranged from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered.

Excretion

The elimination of serum romiplostim is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations of romiplostim and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed after weekly administration of 3 µg/kg Nplate for 6 weeks.

Special populations

Elderly

The pharmacokinetic profile has not been assessed in the elderly.

Paediatric

Pharmacokinetic data of romiplostim were collected from two studies in 21 paediatric subjects with ITP. In Study 6 (20060195), romiplostim concentrations were available from 17 subjects at doses ranging from 1 to 10 µg/kg. In Study 8 (20090340), an open-label extension study, an intensive romiplostim concentrations were available from 4 subjects (2 at 7 µg/kg and 2 at 9 µg/kg). Serum concentrations of romiplostim in paediatrics with ITP were within the range

observed in adult ITP subjects receiving the same dose range of romiplostim. Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in paediatric subjects with ITP and are not reliable, nor predictive. The data are insufficient to draw any meaningful conclusion relating to the impact of dose and age on the pharmacokinetics of romiplostim.

Impaired hepatic function

The pharmacokinetic profile has not been assessed in patients with impaired hepatic function.

Impaired renal function

The pharmacokinetic profile has not been assessed in patients with impaired renal function.

Race/ethnicity

Differences in safety and efficacy based on race or ethnicity have not been established.

5.3 Preclinical safety data

Genotoxicity

The genotoxic potential of romiplostim has not been investigated.

Carcinogenicity

The carcinogenic potential of romiplostim has not been investigated. There is a theoretical concern that romiplostim may stimulate the proliferation of existing cancerous cells that express the TPO receptor (see section 4.4 Special warnings and precautions for use, Risk of progression of myeloid malignancies or existing myelodysplastic syndromes (MDS)).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nplate also contains the following ingredients: mannitol, sucrose, histidine, polysorbate 20, and hydrochloric acid-dilute (for pH adjustment).

6.2 Incompatibilities

Nplate should only be reconstituted with sterile Water for Injection. Do not mix with other medicinal product solutions.

Nplate should not be mixed with other medicinal products or given as an infusion. No other medications should be added to solutions containing romiplostim.

When dilution is required (see section 4.2 Dose and method of administration, Table 1), preservative-free sterile 0.9% sodium chloride only must be used. Do not use glucose (5%) in water or sterile Water for Injections. Other diluents have not been tested.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Nplate should be stored at 2°C to 8°C (Refrigerate. Do not freeze). Vials should be kept in their carton to protect from light until time of use.

Reconstituted solutions of Nplate should be stored at 2°C to 8°C (Refrigerate. Do not freeze), protected from light, for up to 24 hours. However, for microbiological reasons, the reconstituted solution should be used as soon as practicable after reconstitution/preparation.

To reduce microbiological hazard, diluted Nplate should be used immediately. If not used immediately, store for no more than

- 4 hours at 25°C in disposable syringes, or
- 4 hours in a refrigerator (2° to 8°C) in the original vials.

6.5 Nature and contents of container

Nplate is available in a pack containing 1 vial of either:

Presentations available in Australia:

- 250 µg/0.5 mL presentation: 375 µg romiplostim; extractable dose per vial is 250 µg in 0.5 mL. An overfill is included in each vial to ensure that 250 µg of romiplostim can be delivered.
- 500 µg/1 mL presentation: 625 µg romiplostim; extractable dose per vial is 500 µg in 1.0 mL. An overfill is included in each vial to ensure that 500 µg of romiplostim can be delivered.

Presentation not available in Australia:

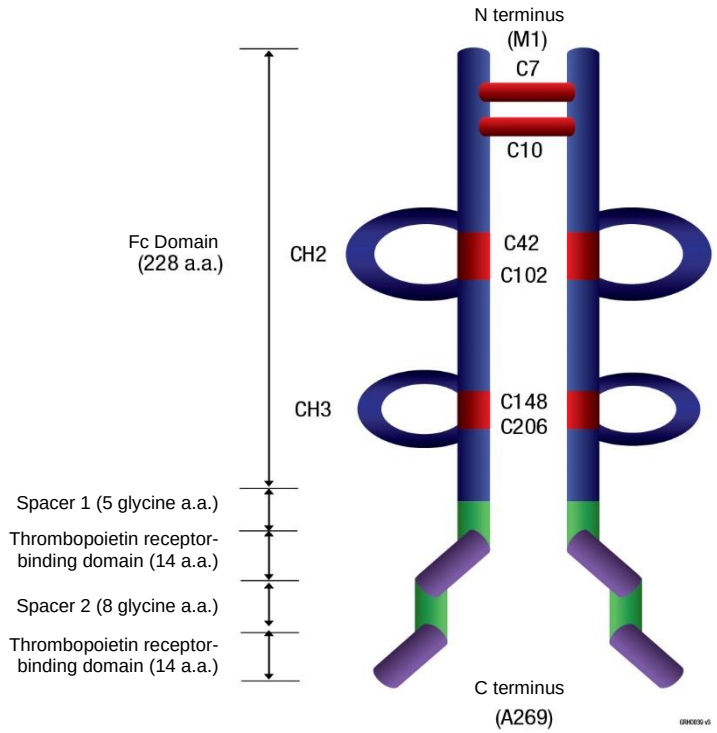
- 125 µg/0.25 mL presentation: 230 µg romiplostim; extractable dose per vial is 125 µg in 0.25 mL. An overfill is included in each vial to ensure that 125 µg of romiplostim can be delivered.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Chemical structure



Romiplostim, a member of the thrombopoietin (TPO) mimetic class, is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as c-Mpl) to increase platelet production. 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. Romiplostim is produced by recombinant DNA technology *in Escherichia coli (E. coli)*.

CAS number

267639-76-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Medicine.

8. SPONSOR

Amgen Australia Pty Ltd

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www.amgenmedinfo.com.au

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of first inclusion in the Australian Register of Therapeutic Goods: 08 August 2008

10. DATE OF REVISION

12 February 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Minor typographical changes
4.6	Removal of information relating to the Lactation Surveillance Program
4.8	Addition of acute myocardial infarction to the post-marketing experience section