1. NAME OF THE MEDICINAL PRODUCT

Nplate 250 micrograms powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nplate 250 micrograms powder for solution for injection

Each vial contains 250 mcg of romiplostim. After reconstitution, a deliverable volume of 0.5 mL solution contains 250 mcg of romiplostim (500 mcg/mL). An additional overfill is included in each vial to ensure that 250 mcg of romiplostim can be delivered.

Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection (powder for injection).

The powder is white.

4. CLINICAL PARTICULARS

Pediatric and adult combined dose Calculator
The marketing of Nplate is subject to a risk management plan (RMP) including a Pediatric and adult combined dose Calculator.

Please ensure you are familiar with this material as it contains important safety information.

4.1 Therapeutic indications

Adults:
Nplate is indicated for the treatment of primary immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

Pediatrics:
Nplate is indicated for the treatment of chronic primary immune thrombocytopenia (ITP) in pediatric patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Treatment should remain under the supervision of a physician who is experienced in the treatment of hematological diseases.

Posology

Nplate should be administered once weekly as a subcutaneous injection.

Initial dose

The initial dose of romiplostim is 1 mcg/kg based on actual body weight.

Dose calculation

The volume of romiplostim to administer is calculated based on body weight, dose required, and concentration of product.

Table 1. Guidelines for calculating individual patient dose and volume of romiplostim to administer

Individual patient dose (mcg)	Individual patient dose (mcg) = weight (kg) × dose in mcg/kg Actual body weight at initiation of treatment should always be used when calculating initial dose. • In adults, future dose adjustments are based on changes in platelet counts only. • In pediatric 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 is ≥ 23 mcg	Reconstitute lyophilized product as described in section 6.6. The resulting concentration is 500 mcg/mL. Volume to administer (mL) = Individual patient dose (mcg)/500 mcg/mL (Round volume to the nearest hundredth mL)
If individual patient dose is < 23 mcg	Dilution is required to ensure accurate dosing. Reconstitute lyophilized product and then dilute the product as described in section 6.6. The resulting concentration is 125 mcg/mL. Volume to administer (mL) = Individual patient dose (mcg)/125 mcg/mL (Round volume to the nearest hundredth mL)
Example	10 kg patient is initiated at 1 mcg/kg of romiplostim. Individual patient dose (mcg) = 10 kg × 1 mcg/kg = 10 mcg Because the dose is < 23 mcg, dilution is required to ensure accurate dosing. Reconstitute lyophilized product and then dilute the product as described in section 6.6. The resulting concentration is 125 mcg/mL. Volume to administer (mL) = 10 mcg/125 mcg/mL = 0.08 mL

Dose adjustments

A subject's actual body weight at initiation of therapy should be used to calculate dose. The once weekly dose of romiplostim should be increased by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50×10^9/L. Platelet counts should be assessed weekly until a stable platelet count (≥ 50×10^9/L for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed monthly thereafter and appropriate dose adjustments made as per the dose adjustment table (see table 2) in order to maintain platelet

counts within the recommended range. See table 2 below for dose adjustment and monitoring. A maximum once weekly dose of 10 mcg/kg should not be exceeded.

Table 2. Dose adjustment guidance based on platelet count

Platelet count ($\times 10^9$/L)	Action
< 50	Increase once weekly dose by 1 mcg/kg
> 150 for two consecutive weeks	Decrease once weekly dose by 1 mcg/kg
> 250	Do not administer, continue to assess the platelet count weekly After the platelet count has fallen to < 150 × 10^9/L, resume dosing with once weekly dose reduced by 1 mcg/kg

Due to the interindividual variable platelet response, in some patients platelet count may abruptly fall below 50 × 10^9/L after dose reduction or treatment discontinuation. In these cases, if clinically appropriate, higher cut-off levels of platelet count for dose reduction (200 × 10^9/L) and treatment interruption (400 × 10^9/L) may be considered according to medical judgment.

A loss of response or failure to maintain a platelet response with romiplostim within the recommended dosing range should prompt a search for causative factors (see section 4.4, Loss of response to romiplostim).

Treatment discontinuation

Treatment with romiplostim should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of romiplostim therapy at the highest weekly dose of 10 mcg/kg.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician, and in non-splenectomized patients this should include evaluation relative to splenectomy. The reoccurrence of thrombocytopenia is likely upon discontinuation of treatment (see section 4.4).

Elderly patients (≥ 65 years)

No overall differences in safety or efficacy have been observed in patients < 65 and ≥ 65 years of age (see section 5.1). Although based on these data no adjustment of the dosing regimen is required for older patients, care is advised considering the small number of elderly patients included in the clinical trials so far.

Pediatric population

The safety and efficacy of romiplostim in children under the age of one year has not been established.

Patients with hepatic impairment

Romiplostim should not be used in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) unless the expected benefit outweighs the identified risk of portal venous thrombosis in patients with thrombocytopenia associated to hepatic insufficiency treated with thrombopoietin (TPO) agonists (see section 4.4).

If the use of romiplostim is deemed necessary, platelet count should be closely monitored to minimize the risk of thromboembolic complications.

Patients with renal impairment

No formal clinical trials have been conducted in these patient populations. Nplate should be used with caution in these populations.

Method of administration

For subcutaneous use.

After reconstitution of the powder, Nplate solution for injection is administered subcutaneously. The injection volume may be very small. Caution should be used during preparation of Nplate in calculating the dose and reconstitution with the correct volume of sterile water for injection. If the calculated individual patient dose is less than 23 mcg, dilution with preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection is required to ensure accurate dosing (see section 6.6). Special care should be taken to ensure that the appropriate volume of Nplate is withdrawn from the vial for subcutaneous administration – a syringe with graduations of 0.01 mL should be used.

Self-administration of Nplate is not allowed for pediatric patients.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to *E. coli* derived proteins.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Reoccurrence of thrombocytopenia and bleeding after cessation of treatment

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with romiplostim. There is an increased risk of bleeding if romiplostim treatment 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 treatment with romiplostim. It is recommended that, if treatment with romiplostim is discontinued, ITP treatment 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.

Increased bone marrow reticulin

Increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines. Increased reticulin may be suggested by morphological

changes in the peripheral blood cells and can be detected through bone marrow biopsy. Therefore, examinations for cellular morphological abnormalities using peripheral blood smear and complete blood count (CBC) prior to and during treatment with romiplostim are recommended. See section 4.8 for information on the increases of reticulin observed in romiplostim clinical trials.

If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow biopsy, and the risk-benefit of romiplostim and alternative ITP treatment options should be re-assessed.

Thrombotic/thromboembolic complications

Thrombotic/thromboembolic events including deep vein thrombosis, pulmonary embolism, and myocardial infarction have been observed with the use of romiplostim in the ITP population. These events have occurred regardless of platelet count (see section 4.8). The incidence of thrombotic/thromboembolic events observed in clinical trials was 6.0% with romiplostim and 3.6% with placebo. Caution should be used when administering romiplostim 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 immobilization, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. It is recommended to monitor patients for signs and symptoms of thrombotic/thromboembolic events and treat promptly as per institutional guidance and standard medical practice.

Cases of thromboembolic events (TEEs), including portal vein thrombosis, have been reported in patients with chronic liver disease receiving romiplostim. Romiplostim should be used with caution in these populations. Dose adjustment guidelines should be followed (see section 4.2).

Medication errors

Medication errors including overdose and underdose have been reported in patients receiving Nplate, dose calculation and dose adjustment guidelines should be followed. In some pediatric patients, accurate dosing relies on an additional dilution step after reconstitution which may increase the risk for medication errors (see section 4.2).

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 4.2, 4.4 and 4.9).

Progression of existing Myelodysplastic Syndromes (MDS)

A positive benefit/risk for romiplostim is only established for the treatment of thrombocytopenia associated with ITP (see section 4.1) and romiplostim must not be used in other clinical conditions associated with thrombocytopenia.

The diagnosis of ITP in adults and elderly patients should have been confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. A bone marrow aspirate and biopsy should normally have been done over the course of the disease and treatment for those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

In adult clinical studies of treatment with romiplostim in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported. In a randomized placebo-controlled trial in MDS subjects, treatment with romiplostim was prematurely stopped due to a numerical excess of disease progression to AML and an increase in circulating blasts greater than 10% in patients receiving romiplostim. Of the cases of MDS disease progression to AML that were observed, patients with RAEB-1 classification of MDS at baseline were more likely to have disease progression to AML compared to lower risk MDS.

Romiplostim must not be used for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP outside of clinical trials.

Loss of response to romiplostim

A loss of response or failure to maintain a platelet response with romiplostim treatment within the recommended dosing range should prompt a search for causative factors, including immunogenicity (see section 4.8) and increased bone marrow reticulin (see above).

Effects of romiplostim on red and white blood cells

Alterations in red (decrease) and white (increase) blood cell parameters have been observed in non-clinical toxicology studies (rat and monkey) as well as in ITP patients. Concurrent anemia and leukocytosis (within a 4-week window) may occur in patients regardless of splenectomy status, but have been seen more often in patients who have had a prior splenectomy. Monitoring of these parameters should be considered in patients treated with romiplostim.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. The potential interactions of romiplostim with co-administered medicinal products due to binding to plasma proteins remain unknown.

Medicinal products used in the treatment of ITP in combination with romiplostim in clinical trials included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining romiplostim with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

Corticosteroids, danazol, and azathioprine use may be reduced or discontinued when given in combination with romiplostim (see section 5.1). Platelet counts should be monitored when reducing or discontinuing other ITP treatments in order to avoid platelet counts below the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of romiplostim in pregnant women.

Studies in animals have shown that romiplostim crossed the placenta and increased fetal platelet counts. Post-implantation loss and a slight increase in peri-natal pup mortality also occurred in animal studies (see section 5.3).

Romiplostim is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether romiplostim/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from romiplostim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There is no data available on fertility.

4.7 Effects on ability to drive and use machines

Nplate has moderate influence on the ability to drive and use machines. In clinical trials, mild to moderate, transient bouts of dizziness were experienced by some patients.

4.8 Undesirable effects

Summary of the safety profile

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, the overall subject incidence of all adverse reactions for romiplostim-treated subjects was 91.5% (248/271). The mean duration of exposure to romiplostim in this study population was 50 weeks.

The most serious adverse reactions that may occur during Nplate treatment include: reoccurrence of thrombocytopenia and bleeding after cessation of treatment, increased bone marrow reticulin, thrombotic/thromboembolic complications, medication errors and progression of existing MDS to AML. The most common adverse reactions observed include hypersensitivity reactions (including cases of rash, urticaria and angioedema) and headache.

Tabulated list of adverse reactions

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each MedDRA system organ class and frequency grouping, undesirable effects are presented in order of decreasing incidence.

MedDRA system organ class	**Very common**	**Common**	**Uncommon**
Infections and infestations	Upper respiratory tract infection Rhinitis***	Gastroenteritis Pharyngitis*** Conjunctivitis*** Ear infection*** Sinusitis***/**** Bronchitis****	Influenza Localized infection Nasopharyngitis

MedDRA system organ class	Very common	Common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Multiple myeloma Myelofibrosis
Blood and lymphatic system disorders		Bone marrow disorder* Thrombocytopenia* Anemia	Aplastic anemia Bone marrow failure Leukocytosis Splenomegaly Thrombocythemia Platelet count increased Platelet count abnormal
Immune system disorders	Hypersensitivity**	Angioedema	
Metabolism and nutrition disorders			Alcohol intolerance Anorexia Decreased appetite Dehydration Gout
Psychiatric disorders		Insomnia	Depression Abnormal dreams
Nervous system disorders	Headache	Dizziness Migraine Paresthesia	Clonus Dysgeusia Hypoesthesia Hypogeusia Neuropathy peripheral Transverse sinus thrombosis
Eye disorders			Conjunctival hemorrhage Accommodation disorder Blindness Eye disorder Eye pruritus Lacrimation increased Papilloedema Visual disturbances
Ear and labyrinth disorders			Vertigo
Cardiac disorders		Palpitations	Myocardial infarction Heart rate increased

MedDRA system organ class	Very common	Common	Uncommon
Vascular disorders		Flushing Deep vein thrombosis	Hypotension Peripheral embolism Peripheral ischemia Phlebitis Thrombophlebitis superficial Thrombosis Erythromelalgia
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain***	Pulmonary embolism*	Cough Rhinorrhea Dry throat Dyspnea Nasal congestion Painful respiration
Gastrointestinal disorders	Upper abdominal pain***	Nausea Diarrhea Abdominal pain Constipation Dyspepsia	Vomiting Rectal hemorrhage Breath odor Dysphagia Gastro-esophageal reflux disease Hematochezia Mouth hemorrhage Stomach discomfort Stomatitis Tooth discoloration
Hepatobiliary disorders			Portal vein thrombosis Increase in transaminase
Skin and subcutaneous tissue disorders		Pruritus Ecchymosis Rash	Alopecia Photosensitivity reaction Acne Dermatitis contact Dry skin Eczema Erythema Exfoliative rash Hair growth abnormal Prurigo Purpura Rash papular Rash pruritic Skin nodule Skin odor abnormal Urticaria

MedDRA system organ class	Very common	Common	Uncommon
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia Muscle spasms Pain in extremity Back pain Bone pain	Muscle tightness Muscular weakness Shoulder pain Muscle twitching
Renal and urinary disorders			Protein urine present
Reproductive system and breast disorders			Vaginal hemorrhage
General disorders and administration site conditions		Fatigue Edema peripheral Influenza like illness Pain Asthenia Pyrexia Chills Injection site reaction Peripheral swelling***	Injection site hemorrhage Chest pain Irritability Malaise Face edema Feeling hot Feeling jittery
Investigations			Blood pressure increased Blood lactate dehydrogenase increased Body temperature increased Weight decreased Weight increased
Injury, poisoning and procedural complications		Contusion	

* See section 4.4
** Hypersensitivity reactions including cases of rash, urticaria, and angioedema
*** Additional adverse reactions observed in pediatric studies
**** Additional adverse reactions observed in adult patients with ITP duration up to 12 months

Adult population with ITP duration up to 12 months

The safety profile of romiplostim 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 romiplostim from among those patients in 9 ITP studies were included (see section 5.1). In this 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 romiplostim patients with ITP duration up to 12 months, but were not observed in those adult patients with ITP duration > 12 months: bronchitis, sinusitis (reported commonly (≥ 1/100 to < 1/10)).

Pediatric population

In the pediatric studies, 282 pediatric ITP subjects were treated with romiplostim in 2 controlled and 3 uncontrolled clinical trials. The median duration of exposure was 65.4 weeks. The overall safety profile was similar to that seen in adults.

The pediatric adverse reactions are derived from each of the pediatric ITP randomized safety set (2 controlled clinical trials) and pediatric ITP safety set (2 controlled and 3 uncontrolled clinical trials) where the subject incidence was at least 5% higher in the romiplostim arm compared to placebo and at least a 5% subject incidence in romiplostim-treated subjects.

The most common adverse reactions in pediatric ITP patients 1 year and older were upper respiratory tract infection, rhinitis, cough, oropharyngeal pain, upper abdominal pain, diarrhea, rash, pyrexia, contusion (reported very commonly (≥ 1/10)), and pharyngitis, conjunctivitis, ear infection, gastroenteritis, sinusitis, purpura, urticaria and peripheral swelling (reported commonly (≥ 1/100 to < 1/10)).

Oropharyngeal pain, upper abdominal pain, rhinitis, pharyngitis, conjunctivitis, ear infection, sinusitis and peripheral swelling were additional adverse reactions observed in pediatric studies compared to those seen in adult studies.

Some of the adverse reactions seen in adults were reported more frequently in pediatric subjects such as cough, diarrhea, rash, pyrexia and contusion reported very commonly (≥ 1/10) in pediatric subjects and purpura and urticaria were reported commonly (≥ 1/100 to < 1/10) in pediatric subjects.

Description of selected adverse reactions

In addition, the reactions listed below have been deemed to be related to romiplostim treatment.

Bleeding events

Across the entire adult ITP clinical program an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (≥ grade 3) bleeding events occurred at platelet counts < 30×10^9/L. All bleeding events ≥ grade 2 occurred at platelet counts < 50×10^9/L. No statistically significant differences in the overall incidence of bleeding events were observed between Nplate and placebo treated patients.

In the two adult placebo-controlled studies, 9 patients reported a bleeding event that was considered serious (5 [6.0%] romiplostim, 4 [9.8%] placebo; Odds Ratio [romiplostim/placebo] = 0.59; 95% CI = (0.15, 2.31)). Bleeding events that were grade 2 or higher were reported by 15% of patients treated with romiplostim and 34% of patients treated with placebo (Odds Ratio; [romiplostim/placebo] = 0.35; 95% CI = (0.14, 0.85)).

In the phase 3 pediatric study, the mean (SD) number of composite bleeding episodes (see section 5.1) was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm.

Thrombocytosis

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 3 events of thrombocytosis were reported, n = 271. No clinical sequelae were reported in association with the elevated platelet counts in any of the 3 subjects.

Thrombocytosis in pediatric subjects occurred uncommonly (≥ 1/1,000 to < 1/100), with a subject incidence of 1 (0.4%). Subject incidence was 1 (0.4%) for either grade ≥ 3 or serious thrombocytosis.

Thrombocytopenia after cessation of treatment

Based on an analysis of all adult ITP patients receiving romiplostim in 4 controlled and 5 uncontrolled clinical trials, 4 events of thrombocytopenia after cessation of treatment were reported, n = 271 (see section 4.4).

Progression of existing Myelodysplastic Syndromes (MDS)

In a randomized placebo-controlled trial in MDS adult subjects treatment with romiplostim was prematurely stopped due to a numerical increase in cases of MDS disease progression to AML and transient increases in blast cell counts in patients treated with romiplostim compared to placebo. Of the cases of MDS disease progression to AML that were observed, patients with RAEB-1 classification of MDS at baseline were more likely to have disease progression to AML (see section 4.4). Overall survival was similar to placebo.

Increased bone marrow reticulin

In adult clinical trials, romiplostim treatment was discontinued in 4 of the 271 patients because of bone marrow reticulin deposition. In 6 additional patients reticulin was observed upon bone marrow biopsy (see section 4.4).

In a pediatric clinical trial (see section 5.1), of the subjects with an evaluable on-study bone marrow biopsy, 5 out of 27 subjects (18.5%) developed increased reticulin at year 1 after exposure to romiplostim (cohort 1) and 17 out of 36 subjects (47.2%) developed increased reticulin at year 2 after exposure to romiplostim (cohort 2). However, no subject showed any bone marrow abnormalities that were inconsistent with an underlying diagnosis of ITP at baseline or on-treatment.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Clinical trials in adult ITP patients examined antibodies to romiplostim and TPO. While 5.7% (60/1,046) and 3.2% (33/1,046) of the subjects were positive for developing binding antibodies to romiplostim and TPO respectively, only 4 subjects were positive for neutralizing antibodies to romiplostim but these antibodies did not cross react with endogenous TPO. Of the 4 subjects, 2 subjects tested negative for neutralizing antibodies to romiplostim at the subject's last timepoint (transient positive) and 2 subjects remained positive at the subject's last timepoint (persistent antibodies). The incidence of pre-existing antibodies to romiplostim and TPO was 3.3% (35/1,046) and 3.0% (31/1,046), respectively.

In pediatric studies, the incidence of binding antibodies to romiplostim at any time was 9.6% (27/282). Of the 27 subjects, 2 subjects had pre-existing binding non-neutralizing romiplostim antibodies at baseline. Additionally, 2.8% (8/282) developed neutralizing antibodies to romiplostim. A total of 3.9% (11/282) subjects had binding antibodies to TPO at any time during romiplostim treatment. Of these 11 subjects, 2 subjects had pre-existing binding non-neutralizing antibodies to TPO. One subject (0.35%) had a weakly positive postbaseline result for neutralizing antibodies against TPO while on-study (consistently negative for anti-romiplostim antibodies) with a negative result at baseline. The subject showed a transient antibody response for neutralizing antibodies against TPO, with a negative result at the subject's last timepoint tested within the study period.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

4.9 Overdose

No adverse effects were seen in rats given a single-dose of 1,000 mcg/kg or in monkeys after repeated administration of romiplostim at 500 mcg/kg (100 or 50 times the maximum clinical dose of 10 mcg/kg, respectively).

In the event of overdose, platelet counts may increase excessively and result in 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 (see sections 4.2 and 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics, ATC code: B02BX04

Mechanism of action

Romiplostim is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as cMpl) 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 2 TPO receptor-binding domains.

Romiplostim has no amino acid sequence homology to endogenous TPO. In pre-clinical and clinical trials no anti-romiplostim antibodies cross reacted with endogenous TPO.

Clinical efficacy and safety

The safety and efficacy of romiplostim have been evaluated for up to 3 years of continuous treatment. In clinical trials, treatment with romiplostim resulted in dose-dependent increases in platelet count. Time to reach the maximum effect on platelet count is approximately 10-14 days, and is independent of the dose. After a single subcutaneous dose of 1 to 10 mcg/kg romiplostim in ITP patients, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2 to 3 weeks period and the response was

variable among patients. The platelet counts of ITP patients who received 6 weekly doses of 1 or 3 mcg/kg of romiplostim were within the range of 50 to 450 × 10^9/L for most patients. Of the 271 patients who received romiplostim in ITP clinical trials, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies.

Results from pivotal placebo-controlled studies

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies in adults with ITP who had completed at least one treatment prior to study entry and are representative of the entire spectrum of such ITP patients.

Study S1 (20030212) evaluated patients who were non-splenectomized and had an inadequate response or were intolerant to prior 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 received 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 × 10^9/L at study entry.

Study S2 (20030105) evaluated patients who were splenectomized and continued to have thrombocytopenia. Patients had been diagnosed with ITP for a 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. 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 × 10^9/L at study entry.

Both studies were similarly designed. Patients (≥ 18 years) were randomized in a 2:1 ratio to receive a starting dose of romiplostim 1 mcg/kg or placebo. Patients received single subcutaneous weekly injections for 24 weeks. Doses were adjusted to maintain (50 to 200 × 10^9/L) platelet counts. In both studies, efficacy was determined by an increase in the proportion of patients who achieved a durable platelet response. The median average weekly dose for splenectomized patients was 3 mcg/kg and for non-splenectomized patients was 2 mcg/kg.

A significantly higher proportion of patients receiving romiplostim achieved a durable platelet response compared to patients receiving placebo in both studies. Following the first 4 weeks of study romiplostim maintained platelet counts ≥ 50 × 10^9/L in between 50% to 70% of patients during the 6 months treatment period in the placebo-controlled studies. In the placebo group, 0% to 7% of patients were able to achieve a platelet count response during the 6 months of treatment. A summary of the key efficacy endpoints is presented below.

Summary of key efficacy results from placebo-controlled studies

	Study 1 non-splenectomized patients		**Study 2 splenectomized patients**		**Combined studies 1 & 2**	
	Romiplostim (n = 41)	Placebo (n = 21)	Romiplostim (n = 42)	Placebo (n = 21)	Romiplostim (n = 83)	Placebo (n = 42)
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	
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)	3.5	7.5	7.9	0.5	7.8	2.5
p-value	< 0.0001		< 0.0001		< 0.0001	
No. (%) patients requiring rescue therapies[d]	8 (20%)	13 (62%)	11 (26%)	12 (57%)	19 (23%)	25 (60%)
(95% CI)	(9%, 35%)	(38%, 82%)	(14%, 42%)	(34%, 78%)	(14%, 33%)	(43%, 74%)
p-value	0.001		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	

	Study 1 non-splenectomized patients		Study 2 splenectomized patients		Combined studies 1 & 2	
	Romiplostim (n = 41)	Placebo (n = 21)	Romiplostim (n = 42)	Placebo (n = 21)	Romiplostim (n = 83)	Placebo (n = 42)

[a] Durable platelet response was defined as weekly platelet count ≥ 50 × 10^9/L for 6 or more times for study weeks 18-25 in the absence of rescue therapies 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 × 10^9/L for 4 or more times during study weeks 2-25 but without durable platelet response. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.
[c] Number of weeks with platelet response is defined as number of weeks with platelet counts ≥ 50 × 10^9/L during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.
[d] Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue medicinal products were not considered for durable platelet response. Rescue therapies allowed in the study were IVIG, platelet transfusions, anti-D immunoglobulin, and corticosteroids.
[e] Stable dose defined as dose maintained within ± 1 mcg/kg during the last 8 weeks of treatment.

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

Study S3 (20080435) was a single-arm, open-label study in adult patients who had an insufficient response (platelet count ≤ 30 × 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 enrollment was 2.2 months (range 0.1 to 6.6). Sixty percent of patients (n = 45) had ITP duration < 3 months and 40% (n = 30) had ITP duration ≥ 3 months. The median platelet count at screening was 20 × 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 of romiplostim over a 12-month treatment period, with individual dose adjustments to maintain platelet counts (50 × 10^9/L to 200 × 10^9/L). During the study, the median weekly romiplostim dose was 3 mcg/kg (25^{th}-75^{th} percentile: 2-4 mcg/kg).

Of the 75 patients enrolled in study 20080435, 70 (93%) had a platelet response ≥ 50 × 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 × 10^9/L for at least 6 months in the absence of romiplostim and any medication for ITP (concomitant or rescue); the median time to onset of maintaining every platelet count ≥ 50 × 10^9/L for at least 6 months was 27 weeks (range 6 to 57).

In an integrated analysis of efficacy, 277 adult patients with ITP duration ≤ 12 months and who received at least one dose of romiplostim from among those patients in 9 ITP studies (inclusive of study S3) were included. Of the 277 romiplostim-treated patients, 140 patients had newly diagnosed ITP (ITP duration < 3 months) and 137 patients had persistent ITP (ITP duration ≥ 3 to ≤ 12 months). The percentage of patients achieving a durable platelet response, defined as at least 6 weekly platelet counts of ≥ 50 × 10^9/L during weeks 18 through

25 of treatment, was 50% (95% CI: 41.4% to 58.6%) for the 140 patients with newly diagnosed ITP and 55% (95% CI: 46.7% to 64.0%) for the 137 patients with persistent ITP. The median (Q1, Q3) percent time with a platelet response ≥ 50 × 10^9/L was 100.0% (70.3%, 100.0%) for patients with newly diagnosed ITP and 93.5% (72.2%, 100.0%) for patients with persistent ITP, respectively. Also, the percentage of patients requiring rescue medications was 47.4% for patients with newly diagnosed ITP and 44.9% for patients with persistent ITP.

Results of studies compared to standard of care (SOC) in non-splenectomized patients

Study S4 (20060131) was an open-label randomized 52 week trial in adult subjects who received romiplostim or medical standard of care (SOC) treatment. Patients had been diagnosed with ITP for a median of 2 years (range 0.01 to 44.2) at the time of study entry. This study evaluated non-splenectomized patients with ITP and platelet counts < 50 × 10^9/L. Romiplostim was administered to 157 subjects by subcutaneous (S.C) injection once weekly starting at a dose of 3 mcg/kg, and adjusted throughout the study within a range of 1-10 mcg/kg in order to maintain platelet counts between 50 and 200 × 10^9/L, 77 subjects received SOC treatment according to standard institutional practice or therapeutic guidelines.

The overall subject incidence rate of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group, with an Odds Ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35).

The overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group, with an Odds Ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61).

Of the 157 subjects randomized to the romiplostim group, three subjects did not receive romiplostim. Among the 154 subjects who received romiplostim, the total median exposure to romiplostim was 52.0 weeks and ranged from 2 to 53 weeks. The most frequently used weekly dose was between 3-5 mcg/kg (25^{th}-75^{th} percentile respectively; median 3 mcg/kg).

Of the 77 subjects randomized to the SOC group, two subjects did not receive any SOC. Among the 75 subjects who received at least one dose of SOC, the total median exposure to SOC was 51 weeks and ranged from 0.4 to 52 weeks.

Reduction in permitted concurrent ITP medical therapies

In both adult 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 (corticosteroids, danazol and/or azathioprine). Twenty-one non-splenectomized and 18 splenectomized patients received on-study ITP medical treatments (primarily corticosteroids) at the start of study. All (100%) splenectomized patients who were receiving romiplostim 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 placebo treated patients. Seventy-three percent of non-splenectomized patients receiving romiplostim 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 (see section 4.5).

Bleeding events

Across the entire adult ITP clinical program an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (≥ grade 3) bleeding events occurred at platelet counts < 30 × 10^9/L. All bleeding events ≥ grade 2 occurred at platelet

counts < 50 × 10^9/L. No statistically significant differences in the overall incidence of bleeding events were observed between romiplostim and placebo treated patients.

In the two adult placebo-controlled studies, 9 patients reported a bleeding event that was considered serious (5 [6.0%] romiplostim, 4 [9.8%] placebo; Odds Ratio [romiplostim/placebo] = 0.59; 95% CI = (0.15, 2.31)). Bleeding events that were grade 2 or higher were reported by 15% of patients treated with romiplostim and 34% of patients treated with placebo (Odds Ratio; [romiplostim/placebo] = 0.35; 95% CI = (0.14, 0.85)).

Pediatric population

The safety and efficacy of romiplostim was evaluated in two placebo-controlled, double-blind studies. Study S5 (20080279) was a phase 3 study with 24 weeks of romiplostim treatment and study S6 (20060195) was a phase 1/2 study with 12 weeks of romiplostim treatment (up to 16 weeks for eligible responders who enter a 4-week pharmacokinetic assessment period).

Both studies enrolled pediatric subjects (≥ 1 year to < 18 years of age) with thrombocytopenia (defined by a mean of 2 platelet counts ≤ 30 × 10^9/L with neither count > 35 × 10^9/L in both studies) with ITP, regardless of splenectomy status.

In study S5, 62 subjects were randomized in a 2:1 ratio to receive romiplostim (n = 42) or placebo (n = 20) and stratified into 1 of 3 age cohorts. The starting dose of romiplostim 1 mcg/kg and doses were adjusted to maintain (50 to 200 × 10^9/L) platelet counts. The most frequently used weekly dose was 3-10 mcg/kg and the maximum allowed dose on-study was 10 mcg/kg. Patients received single subcutaneous weekly injections for 24 weeks. Of those 62 subjects, 48 subjects had ITP > 12 months of duration (32 subjects received romiplostim and 16 subjects received placebo).

The primary endpoint was the incidence of durable response, defined as achieving at least 6 weekly platelet counts of ≥ 50 × 10^9/L during weeks 18 through 25 of treatment. Overall, a significant greater proportion of subjects in the romiplostim arm achieved the primary endpoint compared with subjects in the placebo arm (p = 0.0018). A total of 22 subjects (52%) had durable platelet response in the romiplostim arm compared with 2 subjects (10%) in the placebo arm: ≥ 1 to < 6 years 38% versus 25%; ≥ 6 to < 12 years 56% versus 11%; ≥ 12 to < 18 years 56% versus 0%.

In the subset of subjects with ITP > 12 months of duration, the incidence of durable response was also significantly greater in the romiplostim arm compared with the placebo arm (p = 0.0022). A total of 17 subjects (53.1%) had durable platelet response in the romiplostim arm compared with 1 subject (6.3%) in the placebo arm: ≥ 1 to < 6 years 28.6% versus 25%; ≥ 6 to < 12 years 63.6% versus 0%; ≥ 12 to < 18 years 57.1% versus 0%.

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 was 1.9 (4.2) for the romiplostim 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 romiplostim arm and 0.5 (0, 4.5) in the placebo arm. In the subset of subjects with ITP > 12 months of duration, the mean (SD) number of composite bleeding episodes was 2.1 (4.7) for the romiplostim arm and 4.2 (7.5) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.0 (0, 4) in the placebo arm. Because the statistical testing for the incidence of rescue medication use was not significant, no statistical test was done for the number of composite bleeding episodes endpoint.

In study S6, 22 subjects were randomized in a 3:1 ratio to receive romiplostim (n = 17) or placebo (n = 5). Doses were increased in increments of 2 mcg/kg every 2 weeks and the target platelet count was $\geq 50 \times 10^9$/L. Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0008). Of those 22 subjects, 17 subjects had ITP > 12 months of duration (14 subjects received romiplostim and 3 subjects received placebo). Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0147).

Pediatric subjects who had completed a prior romiplostim study (including study S5) were allowed to enroll in study S7 (20090340), an open-label extension study evaluating the safety and efficacy of long-term dosing of romiplostim in thrombocytopenic pediatric subjects with ITP.

A total of 66 subjects were enrolled in this study, including 54 subjects (82%) who had completed study S5. Of these, 65 subjects (98.5%) received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg). Of the 66 subjects enrolled in the study, 63 subjects had ITP > 12 months of duration. All the 63 subjects received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 138.0 weeks (91.1 weeks, 186.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg).

Across the study, the overall subject incidence of platelet response (1 or more platelet count $\geq 50 \times 10^9$/L in the absence of rescue medication) was 93.8% (n = 61) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on-study was 34.0 months (24.0 months, 46.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

In the subset of subjects with ITP > 12 months of duration, the overall subject incidence of platelet response was 93.7% (n = 59) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on-study was 35.0 months (23.0 months, 47.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

A total of 31 subjects (47.7%) used concurrent ITP therapy during the study including 23 subjects (35.4%) who used rescue medication and 5 subjects (7.7%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 30.8% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

In the subset of subjects with ITP > 12 months of duration, 29 subjects (46.0%) used concurrent ITP therapy during the study including 21 subjects (33.3%) who used rescue medication and 5 subjects (7.9%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 31.7% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

The subject prevalence of rescue medication use showed a trend towards a reduction over the course of the study: from 24.6% (weeks 1 to 12) to < 13.0% (weeks 13 to 216), then 0% after week 216 until the end of the study. Similar reduction of the subject prevalence of rescue medication over the course of the study was seen in the subset of subjects with ITP > 12 months of duration: from 25.4% (weeks 1 to 12) to ≤ 13.1% (weeks 13 to 216), then 0% after week 216 until the end of the study.

Study S8 (20101221) was a phase 3, long-term, single-arm, open-label, multicenter study conducted in 203 pediatric patients with ITP diagnosed for at least 6 months and who received at least 1 prior ITP therapy (excluding romiplostim) or were ineligible for other ITP therapies. Romiplostim was administered weekly by subcutaneous injection starting at a dose of 1 mcg/kg with weekly increments to a maximum dose of 10 mcg/kg to reach a target platelet count between 50×10^9/L and 200×10^9/L. The median age of the patients was 10 years (range 1 to 17 years) and the median duration of treatment were 155.9 (range 8.0 to 163.0) weeks.

The mean (SD) and median percentage of time with a platelet response (platelet count $\geq 50 \times 10^9$/L) within the first 6 months of initiation of romiplostim without rescue medication use for the past 4 weeks was 50.57% (37.01) and 50.0%, respectively. Sixty (29.6%) subjects overall received rescue medications. Rescue medications (i.e., corticosteroids, platelet transfusions, IVIG, azathioprine, anti-D immunoglobulin, and danazol) were permitted.

Study S8 also evaluated bone marrows for reticulin and collagen formation as well as for abnormalities in pediatric patients with ITP receiving romiplostim treatment. The modified Bauermeister grading scale was used for reticulin and collagen assessments, whereas cytogenetics and fluorescence *in situ* hybridization (FISH) were used to evidence bone marrow abnormalities. Based on cohort assignment at the time of study enrollment, patients were evaluated for bone marrow reticulin and collagen at year 1 (cohort 1) or year 2 (cohort 2) in comparison to the baseline bone marrow at the start of the study. From the total of 79 patients enrolled in the 2 cohorts, 27 of 30 (90%) patients in cohort 1 and 36 of 49 (73.5%) patients in cohort 2 had evaluable on-study bone marrow biopsies. Increased reticulin fiber formation was reported for 18.5% (5 of 27) of patients in cohort 1 and 47.2% (17 of 36) of patients in cohort 2. No patients in either cohort developed collagen fibrosis or a bone marrow abnormality that was inconsistent with an underlying diagnosis of ITP.

5.2 Pharmacokinetic properties

The pharmacokinetics of romiplostim involved target-mediated disposition, which is presumably mediated by TPO receptors on platelets and other cells of the thrombopoietic lineage such as megakaryocytes.

Absorption

After subcutaneous administration of 3 to 15 mcg/kg romiplostim, maximum romiplostim serum levels in ITP patients were obtained after 7-50 hours (median 14 hours). The serum concentrations varied among patients and did not correlate with the dose administered. Romiplostim serum levels appear inversely related to platelet counts.

Distribution

The volume of distribution of romiplostim following intravenous administration of romiplostim decreased nonlinearly from 122, 78.8 to 48.2 mL/kg for intravenous doses of 0.3, 1.0 and 10 mcg/kg, respectively in healthy subjects. This non-linear decrease in volume of distribution is in line with the (megakaryocyte and platelet) target-mediated binding of romiplostim, which may be saturated at the higher doses applied.

Elimination

Elimination half-life of romiplostim in ITP patients ranged from 1 to 34 days (median, 3.5 days).

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 and *vice versa*. In another ITP clinical trial, no accumulation in serum concentrations was observed after 6 weekly doses of romiplostim (3 mcg/kg).

Special populations

Pharmacokinetics of romiplostim in patients with renal and hepatic impairment has not been investigated. Romiplostim pharmacokinetics appear not affected by age, weight and gender to a clinically significant extent.

Pediatric population

Pharmacokinetic data of romiplostim were collected from two studies in 21 pediatric subjects with ITP. In study S6 (20060195), romiplostim concentrations were available from 17 subjects at doses ranging from 1 to 10 mcg/kg. In Study S7 (20090340), intensive romiplostim concentrations were available from 4 subjects (2 at 7 mcg/kg and 2 at 9 mcg/kg). Serum concentrations of romiplostim in pediatrics 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 pediatric subjects with ITP and are not reliable and predictive. However, the data are insufficient to draw any meaningful conclusion relating to the impact of dose and age on the pharmacokinetics of romiplostim.

5.3 Preclinical safety data

Multiple dose romiplostim toxicology studies were conducted in rats for 4 weeks and in monkeys for up to 6 months. In general, effects observed during these studies were related to the thrombopoietic activity of romiplostim and were similar regardless of study duration. Injection site reactions were also related to romiplostim administration. Myelofibrosis has been observed in the bone marrow of rats at all tested dose levels. In these studies, myelofibrosis was not observed in animals after a 4-week post-treatment recovery period, indicating reversibility.

In 1-month rat and monkey toxicology studies, a mild decrease in red blood cell count, hematocrit and hemoglobin was observed. There was also a stimulatory effect on leukocyte production, as peripheral blood counts for neutrophils, lymphocytes, monocytes, and eosinophils were mildly increased. In the longer duration chronic monkey study, there was no effect on the erythroid and leukocytic lineages when romiplostim was administered for 6 months where the administration of romiplostim was decreased from thrice weekly to once weekly. Additionally, in the phase 3 pivotal studies, romiplostim did not affect the red blood cell and white blood cells lineages relative to placebo treated subjects.

Due to the formation of neutralizing antibodies pharmacodynamic effects of romiplostim in rats were often decreasing at prolonged duration of administration. Toxicokinetic studies showed no interaction of the antibodies with the measured concentrations. Although high doses were tested in the animal studies, due to differences between the laboratory species and humans with regard to the sensitivity for the pharmacodynamic effect of romiplostim and the effect of neutralizing antibodies, safety margins cannot be reliably estimated.

Carcinogenesis

The carcinogenic potential of romiplostim has not been evaluated. Therefore, the risk of potential carcinogenicity of romiplostim in humans remains unknown.

Reproductive toxicology

In all developmental studies neutralizing antibodies were formed, which may have inhibited romiplostim effects. In embryo-fetal development studies in mice and rats, reductions in maternal body weight were found only in mice. In mice there was evidence of increased post-implantation loss. In a prenatal and postnatal development study in rats an increase of the duration of gestation and a slight increase in the incidence of peri-natal pup mortality was found. Romiplostim is known to cross the placental barrier in rats and may be transmitted from the mother to the developing fetus and stimulate fetal platelet production. Romiplostim had no observed effect on the fertility of rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sucrose
L-histidine
Hydrochloric acid (for pH adjustment)
Polysorbate 20

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After reconstitution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C and for 24 hours at 2°C – 8°C, when protected from light and kept in the original vial.

From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25°C or 24 hours in a refrigerator (2°C – 8°C), protected from light.

After dilution: Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C when the diluted product was held in a disposable syringe, or 4 hours in a refrigerator (2°C – 8°C) when the diluted product was held in the original vial.

From a microbiological point of view, the diluted medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 4 hours at 25°C in disposable syringes, or 4 hours in a refrigerator (2°C – 8°C) in the original vials, protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.
May be removed from the refrigerator for a period of 30 days at room temperature (up to 25°C) when stored in the original carton.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mL single-dose vial (type 1 clear glass) with a stopper (chlorobutyl rubber), seal (aluminum) and a flip-off cap (polypropylene).

Carton containing 1 vial of romiplostim.

6.6 Special precautions for disposal and other handling

Reconstitution

Nplate is a sterile but unpreserved medicinal product and is intended for single-use only. Nplate should be reconstituted in accordance with good aseptic practice.

Nplate 250 micrograms powder for solution for injection

Nplate 250 micrograms powder for solution for injection should be reconstituted with 0.72 mL sterile water for injections, yielding a deliverable volume of 0.5 mL. An additional overfill is included in each vial to ensure that 250 mcg of romiplostim can be delivered (see vial content table below).

Vial Content:

Nplate single-use vial	**Total vial content of romiplostim**		**Volume of sterile water for injection**		**Deliverable product and volume**	**Final concentration**
250 mcg	375 mcg	+	0.72 mL	=	250 mcg in 0.50 mL	500 mcg/mL

Sterile water for injections only should be used when reconstituting the medicinal product. Sodium chloride solutions or bacteriostatic water should not be used when reconstituting the medicinal product.

Water for injections should be injected into the vial. The vial contents may be swirled gently and inverted during dissolution. The vial should not be shaken or vigorously agitated. Generally, dissolution of Nplate takes less than 2 minutes. Visually inspect the solution for particulate matter and discoloration before administration. The reconstituted solution should be clear and colorless and should not be administered if particulate matter and/or discoloration are observed.

For the storage condition after reconstitution of the medicinal product, see section 6.3.

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

Dilution (required when the calculated individual patient dose is less than 23 mcg)

Initial reconstitution of romiplostim with designated volumes of sterile water for injections results in a concentration of 500 mcg/mL in all vial sizes. If the calculated individual patient dose is less than 23 mcg (see section 4.2), an additional dilution step to 125 mcg/mL with **preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection** is required to ensure accurate volume (see table below).

Dilution Guidelines:

Nplate single-use vial	Add this volume of preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection to the **reconstituted vial**	Concentration after dilution
250 mcg	2.25 mL	125 mcg/mL

Preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection only must be used for dilution. Dextrose (5%) in water or sterile water for injection should not be used for the dilution.

No other diluents have been tested.

For the storage condition after dilution of the reconstituted medicinal product, see section 6.3.

7. MANUFACTURER

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The Netherlands

8. LICENSE HOLDER

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Revised in October 2025.