Report on the Deliberation Results

December 1, 2010
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Romiplate for S.C. Injection 250 μg
[Non-proprietary name]	Romiplostim (Genetical Recombination) (JAN*)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	March 29, 2010

[Results of deliberation]
In the meeting held on November 24, 2010, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 10 years, and neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug.

[Conditions for approval]
Since the product has only been studied in a limited number of patients in Japan, the applicant is required to conduct a post-marketing drug use-results survey in all the patients treated until data from a certain number of patients have been accumulated in order to identify the background information of patients treated with the product. At the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

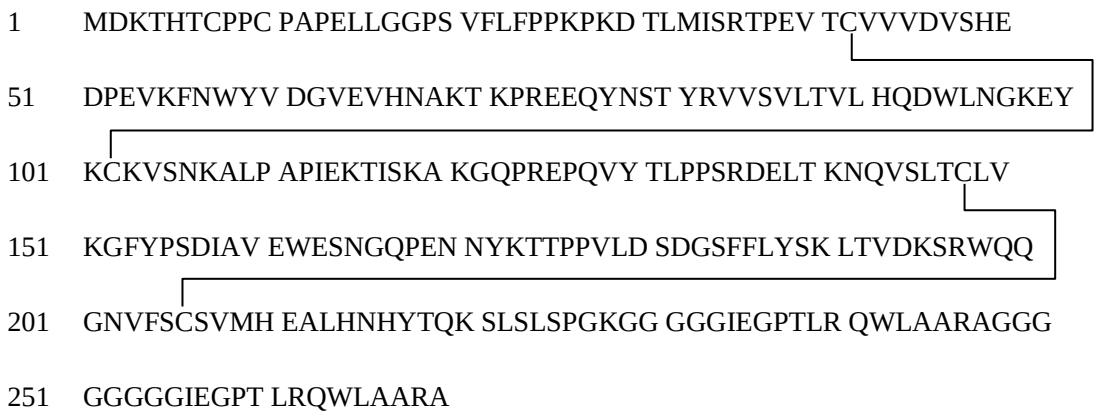
November 17, 2010
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Romiplate for Subcutaneous Injection (planned to be changed to Romiplate for S.C. Injection 250 μg)
[Non-proprietary name]	Romiplostim (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	March 29, 2010
[Dosage form/Strength]	Lyophilized powder for solution for subcutaneous injection: Each vial contains 375 μg of Romiplostim (Genetical Recombination).
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Entity] Romiplostim is a recombinant Fc-peptide fusion protein composed of human IgG1 Fc region in positions 2-228 and peptide containing human thrombopoietin receptor binding sequences in positions 229-269. Romiplostim is a protein composed of 2 subunit molecules consisting of 269 amino acid residues each.

Structural formula:



Complete amino acid sequence of Romiplostim (Genetical Recombination)

Molecular formula:	$C_{2634}H_{4086}N_{722}O_{790}S_{18}$
Molecular weight:	59,085

[Items warranting special mention]
Orphan drug (Notification No. 0202-24 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated February 2, 2010)

[Reviewing office] Office of New Drug II

Review Results

November 17, 2010

[Brand name]	Romiplate for Subcutaneous Injection (planned to be changed to Romiplate for S.C. Injection 250 μg)
[Non-proprietary name]	Romiplostim (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	March 29, 2010

[Results of review]

Based on the submitted data, it is concluded that the efficacy of the drug product in patients with chronic idiopathic thrombocytopenic purpura has been demonstrated, and its safety is acceptable in view of its observed benefits. It is considered important to collect, via post-marketing surveillance, information regarding occurrence of bleeding, thromboembolism, increased bone marrow reticulin, myelofibrosis, myelodysplastic syndrome, etc., during the long-term treatment.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]	Chronic idiopathic thrombocytopenic purpura
[Dosage and administration]	The usual initial adult dosage is 1 μg/kg of Romiplostim (Genetical Recombination) administered subcutaneously. After starting the treatment, it should be administered once weekly subcutaneously at the dose depending on the patient's platelet count and other symptoms, and it should be injected subcutaneously once weekly. The maximum dose is 10 μg/kg once weekly.
[Conditions for approval]	Since the product has only been studied in a limited number of patients in Japan, the applicant is required to conduct a post-marketing drug use-results survey of all the patients treated until data from a certain number of patients have been accumulated in order to understand the background information of patients treated with the product. At the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

Review Report (1)

November 1, 2010

I. Product Submitted for Registration

[Brand name] Romiplate for Subcutaneous Injection (planned to be changed to Romiplate for S.C. Injection 250 μg)

[Non-proprietary name] Romiplostim (Genetical Recombination)

[Name of applicant] Kyowa Hakko Kirin Co., Ltd.

[Date of application] March 29, 2010

[Dosage form/Strength] Lyophilized powder for solution for subcutaneous injection: Each vial contains 375 μg of Romiplostim (Genetical Recombination).

[Proposed indication] Thrombocytopenia in adult patients with chronic immune-mediated (idiopathic) thrombocytopenic purpura

[Proposed dosage and administration]

The initial dosage for adults is 1 μg/kg of Romiplostim (Genetical Recombination) (on a body weight basis) administered subcutaneously once weekly. Then, the dose may be adjusted with reference to the following table so that the platelet count can be maintained within the target range of 50,000 to 200,000/μL. The maximum dose is 10 μg/kg once weekly.

Dose adjustment table

Platelet count	Dose adjustment
<50,000/μL	Increase the dose weekly by 1 μg/kg.
>200,000/μL	Decrease the dose by 1 μg/kg biweekly if the platelet counts are in this range for 2 consecutive weeks.
>400,000/μL	Suspend the administration. Resume the administration at the dose decreased by 1 μg/kg if the platelet count has decreased to ≤200,000/μL.

[Items warranting special mention]

Orphan drug (Notification No. 0202-24 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated February 2, 2010)

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

A summary of data submitted in this application and an outline of the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries, etc.

Romiplostim (Genetical Recombination) (hereinafter referred to as romiplostim) is a thrombopoietin (TPO) receptor agonist developed by Amgen Inc. (the U.S.). The compound has 2 single-chain subunits, joined by disulfide bonds, each consisting of a human immunoglobulin IgG1 Fc domain linked to a peptide chain (thrombopoietin mimetic peptide [TMP] chain) containing 2 TPO receptor-binding domains. Romiplostim activates the TPO receptor to enhance growth and differentiation of cells in the maturation process from bone-marrow precursor cells to megakaryocytes, resulting in increased platelet production.

Romiplostim was first approved overseas in Australia in July 2008 for the indication of

thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP). As of July 2010, it has been approved in 27 countries including the U.S. and major European countries.

In Japan, the development of romiplostim was initiated by Amgen Inc. in 2004. Kyowa Hakko Kirin Co., Ltd. has recently submitted an application for its marketing approval based on Japanese and foreign clinical study data, etc. In Japan, romiplostim was designated as an orphan drug in August 2006.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

The drug substance is a recombinant fusion protein ($C_{2634}H_{4086}N_{722}O_{790}S_{18}$; molecular weight, 59,085) having 2 single-chain peptides, joined by disulfide bonds, each consisting of a human immunoglobulin IgG1 Fc domain linked at the C-terminus to a TMP chain comprised of 14 amino acid residues via a peptide chain comprised of 8 glycine residues with a peptide chain comprised of 5 glycine residues. It is produced in *Escherichia coli* (*E. coli*). Each single chain is comprised of 269 amino acid residues with no glycosylation sites. There are 2 disulfide bonds between the chains and 2 within each single chain.

2.A.(1).1) Manufacturing process

2.A.(1).1).(a) Gene expression construct and cell banks

An Fc domain gene segment was prepared from *E. coli*-derived DNA containing a gene segment of human IgG1 heavy chain by Polymerase Chain Reaction (PCR). Additionally, a TMP gene segment having a TMP-repeated structure was chemically synthesized. [redacted].

[redacted]. A master cell bank (MCB) was prepared from this seed cell line, and a working cell bank (WCB) was prepared from the MCB.

2.A.(1).1).(b) Characterization and control of cell banks

The MCB, WCB and cells cultured up to the limit of *in vitro* cell age (CAL) were subjected to purity and characterization tests.

[redacted]. The plasmid structure of the WCBs was identified by restriction enzyme digestion analysis.

[redacted].

[redacted].

Considering how frequently WCB is being used and the number of its remaining vials, a new WCB is prepared as needed so that the drug substance can be continuously manufactured. Alternatively, when the quality of the WCB becomes questionable, the new WCB should be prepared. The WCB is newly established from the MCB according to the current WCB preparation procedure and subjected to the above purity and characterization tests to confirm whether the cells can be qualified as a WCB.

2.A.(1).1).(c) Manufacturing process

- Pre-culture process: The WCB is thawed and cultured using the pre-culture medium.
- Main culture process: [redacted].
- Bacteria processing process: [redacted].
- Thawing and solubilization process: The [redacted]-time washed IBs (DWIB) is thawed and solubilized with a solubilizing buffer.
- Oxidization process: [redacted].
- Concentration and buffer exchange process: [redacted].
- Acid precipitation and clarification process: [redacted].
- Purification process 1: [redacted].
- Purification process 2: [redacted].
- Purification process 3: [redacted].
- Buffer exchange and concentration adjustment process: [redacted].
- Filtration and filling process: [redacted].

The critical processes include the main culture process, purification process 2, purification process 3, and buffer exchange and concentration adjustment process. In-process control tests

include checking the contamination by heterologous microorganisms at the end of culture in the main culture process and the amount of host-derived proteins in the purification process 3. [redacted].

Process validation of the manufacturing process of the drug substance was conducted at an actual production scale. The validation demonstrated that the following parameters met the pre-established acceptance criteria, indicating that each manufacturing process is consistently and appropriately controlled.

- Pre-culture process: [redacted]
- Main culture process: [redacted]
- Bacteria processing process: [redacted]
- Thawing and solubilization process: Process yield
- Oxidization process: [redacted]
- Concentration and buffer exchange process: Process yield and electrical conductivity after buffer exchange
- Acid-induced precipitation and precipitation process: Process yield, the percentage of main peak area as determined by reversed-phase liquid chromatography (HPLC), the percentage of main peak area as determined by gel filtration HPLC, and the percentage of main peak area as determined by cation-exchange HPLC
- Purification processes 1, 2, and 3: [redacted]
- Buffer exchange and concentration adjustment process: Absorbance (of filtered solution at buffer exchange and after concentration adjustment), the pH and electrical conductivity of the crude protein extract, romiplostim concentration, process yield, L-histidine concentration, purified sucrose concentration, D-mannitol concentration, and bioburden
- Filtration and filling process: [redacted]

The level of impurities removed in the manufacturing process was evaluated at an actual production scale. Each process control was confirmed to consistently remove process-related impurities and product-related impurities [for the details of these impurities, see 2.A.(1).2).(c) Impurities]. Additionally, the maximum lifespan of the column packing materials in the purification processes 1, 2, and 3 and of the membrane for concentration and buffer exchange in the concentration and buffer exchange process were determined at the laboratory and actual production scales. The column packing material in the purification process [redacted] can be reused [redacted] times, the column packing materials in the purification processes [redacted] and [redacted], [redacted] times, and the membrane for concentration and buffer exchange in the concentration and buffer exchange process, [redacted] times.

The stability of the critical intermediate (DWIB) was tested. The DWIB was stable at [redacted]°C ± [redacted]°C for [redacted] months.

2.A.(1).1).(d) Safety evaluation of adventitious agents

Tryptone (derived from cow milk made in Australia, New Zealand, and the U.S.) used in preparation of the WCB is a biological material that conforms to the Standards for Biological Ingredients (MHLW Ministerial Announcement No. 210, dated May 20, 2003).

2.A.(1).1).(e) History of changes in manufacturing process and comparability between pre-change and post-change drug substance

The major changes in the manufacturing process of the drug substance in the course of development are presented below.

- Change from P1-pilot method to P1-ATO method:

- Change from P1-ATO method to P2-ATO method:

  Container size in the filtration and filling process

- Change from P2-ATO method to P2-ACO method (commercial production):

Prior to the change from the P1-pilot method to the P1-ATO method, the comparability of the drug substances before and after the change was assessed by the following tests. As a result of these tests, the applicant determined that the drug substances were comparable.

Prior to the changes from the P1-ATO method to the P2-ATO method and from the P2-ATO method to the P2-ACO method, the comparability of the drug substances before and after the

change was assessed by the following tests. As a result of these tests, the applicant determined that these drug substances were comparable. In changing from the P2-ATO method to the P2-ACO method, the amount of romiplostim in the DWIB (reversed-phase HPLC), as well as the purity (gel filtration HPLC, cation-exchange HPLC, reversed-phase HPLC), host cell-derived protein (ELISA), host cell-derived DNA (quantitative PCR), and the process yield for the other process intermediates were also evaluated. Based on these results, the applicant determined that the pre-change and post-change drug substances were comparable.

Description (visual inspection), identification (ELISA), pH (pH determination), purity (gel filtration HPLC, cation-exchange HPLC, reversed-phase HPLC), endotoxins (bacterial endotoxins test), biological activity ([redacted]), protein concentration (UV), electrophoretic pattern (SDS-PAGE), host cell-derived protein (ELISA), host cell-derived DNA (quantitative PCR), bioburden (microbial limit test), amino acid sequence (2 types of peptide mapping: reversed-phase HPLC chromatogram of peptide digested by lysyl endopeptidase [Lys-C], Lys-C map; reversed-phase HPLC chromatogram of peptide digested by protease V8 [Glu-C] after reductive alkylation, Glu-C map), disulfide bond (Lys-C map), molecular weight (mass spectrometry), methionine oxidation (Lys-C map), molecular size isomer (SDS-PAGE, gel filtration HPLC), secondary structure (circular dichroism [CD] spectrum [far ultraviolet], Fourier transform infrared spectroscopy), tertiary structure (CD spectrum [near ultraviolet], fluorescence spectrum), binding to fetal Fc receptor (Fc-Rn) (surface plasmon resonance), TPO receptor-binding (surface plasmon resonance), and stability (long-term, accelerated, and stress testing)

2.A.(1).2) Characterization

The following tests were performed for characterization of the drug substance.

2.A.(1).2).(a) Structure and composition

- Primary structure
  - Lys-C map, the results of mass spectrometry after separation of Lys-C-digested peptides by reversed-phase HPLC (Lys-C map-MS), Glu-C map, and the results of mass spectrometry after separation of Glu-C-digested peptides by reversed-phase HPLC (Glu-C map-MS) demonstrated that the whole amino acid sequence was consistent with that estimated from the cDNA base sequence. Glu-C map revealed no change in the N-terminal sequence.
  - Protein sequence analysis (Edman degradation) and HPLC-tandem mass spectrometry (LC/MS/MS) of Lys-C-digested peptide and Glu-C-digested peptides identified the whole amino acid sequence.

- Higher-order structure
  - The Lys-C map (non-reducing and reducing conditions) and protein sequence analysis indicated 6 cysteine residues within each single chain, with 4 in intrachain and 2 in interchain disulfide bonds. Free sulfhydryl analysis using Ellman's reagent demonstrated that romiplostim contains [redacted] ± [redacted] mol of free sulfhydryl group per mol.
  - Far ultraviolet CD spectroscopy and Fourier transform infrared spectroscopy indicated a β sheet structure of romiplostim similar to the IgG Fc domain.
  - Near ultraviolet CD spectroscopy revealed λmin = 292 nm due to contribution of tryptophan residues, λmax = 289 nm and a shoulder of 280 nm due to contribution of tryptophan residues and tyrosine residues, and a fine peak between the wavelengths of 255 and 280 nm due to contribution of phenylalanine residues and tyrosine residues. The overall signal was downwardly shifted because of contribution of disulfide bonds.

- Fluorescence spectroscopy showed λmax = 342 nm, indicating that tryptophan residues are present in a hydrophilic environment and partially in contact with the solvent.

- Isomers
  - [redacted].
  - [redacted]. The biological activity of the isomer with an aberrant disulfide bond, which formed no aggregate during the analyses, was measured. It was approximately [redacted]% of that of the reference material.
  - [redacted].

    Gel filtration HPLC of the drug product detected peaks of high-molecular-weight isomers (HMWS). The peaks were aggregations formed by noncovalent bonding of romiplostim and by noncovalent bonding of romiplostim and molecules of [redacted] to [redacted] kDa as determined by sedimentation velocity ultracentrifugation, non-modified gel filtration HPLC, modified gel filtration HPLC (reducing and non-reducing conditions), SDS-PAGE (reducing and non-reducing conditions), and dynamic light scattering.

- Other physicochemical characterization
  - The reducing and non-reducing molecular weights of romiplostim as determined by electrospray ionization mass spectrometry were consistent with their theoretical molecular weights.
  - The transition temperatures denaturing the Fc core hinge (CH) 2 domain and Fc CH3 domain were approximately [redacted]°C and [redacted]°C, respectively, as determined by differential scanning calorimetry.

- Biological characterization
  - The TPO receptor-binding affinity of romiplostim was assessed by surface plasmon

resonance. The dissociation constant (K_D) of romiplostim was approximately [redacted] pmol/L.

- [redacted].
- The FcRn-binding affinity of romiplostim was assessed by surface plasmon resonance based on inhibition of human Fc binding to FcRn. The inhibitory effect of romiplostim was dose-dependent. The concentration of romiplostim required to inhibit cell proliferation by 50% (IC_{50}) was approximately [redacted] nmol/L.
- In addition to the above biological characteristics, signaling via TPO receptors and phosphorylation of Janus kinase 2 (JAK2), and the colony-forming capability of megakaryocytes were investigated [see 3.(i) Summary of pharmacology studies].

2.A.(1).2).(b) Product-related substances

[redacted].

2.A.(1).2).(c) Impurities

- Process-related impurities

  [redacted].

- Product-related impurities

  [redacted].

2.A.(1).3) Specifications

The proposed specifications (test methods) for the drug substance include description (visual inspection), identification (ELISA), pH (pH determination), purity (gel filtration HPLC, cation-exchange HPLC, reversed-phase HPLC), endotoxins (bacterial endotoxins test), microbial limit test (viable cell count), biological activity ([redacted]), and assay (UV).

2.A.(1).4) Stability of drug substance

A long-term testing (-30°C, 48 months), accelerated testing ([redacted]°C, [redacted] months), and stress testing ([redacted]°C, [redacted] months) were conducted using 3 batches of the drug substance manufactured on a commercial scale. In all of these tests, the drug substance was stored in a fluorinated ethylene propylene bottle. The test items include the description, pH, purity, biological activity, assay, and electrophoretic pattern of the drug substance. The drug substance was stable without any change over time in any of these tests in the long-term testing. [redacted].

Based on the above stability test results, a shelf life of 48 months has been proposed for the drug substance when stored at -30°C in a fluorinated ethylene propylene bottle.

2.A.(2) Drug product

2.A.(2).1) Formulation development

The drug product is a lyophilized injection containing 375 μg of the drug substance per vial. It contains 30 mg of D-mannitol as a diluent, 15 mg of sucrose as a stabilizer, 1.2 mg of L-histidine as a buffering agent, 0.03 mg of polysorbate 20 as a stabilizer, and an appropriate amount of diluted hydrochloric acid as a pH adjuster. In order to prepare a maximum injectable amount (0.5 mL), 0.72 mL of water for injection is used to reconstitute per vial. The final volume of reconstituted solution becomes 0.75 mL, 50% overfilling relative to the labeled amount (250 μg).

[redacted].

2.A.(2).2) Manufacturing process

The manufacturing process of the drug product is presented below.

- Drug substance thawing process: The frozen drug substance is thawed at [redacted]°C.
- Drug solution preparation process: [redacted].
- Sterile filtration process: [redacted].
- Filling process: The sterile-filtered working solution is filled in a 5-mL colorless glass vial and loosely capped with a rubber stopper.
- Lyophilization process: The loosely capped vial is lyophilized and fully capped with a rubber stopper.
- Crimping process: The vial is crimped using a rotary cap-crimping machine (intermediate product).
- Packaging process: The intermediate product is labeled and placed in a paper box (final product).
- Test and storage process: The final product is stored at 2°C to 8°C until subjected to release tests and release.

The critical processes of the manufacturing process include the drug solution preparation process, sterile filtration process, filling process, and lyophilization process. In-process control includes pH and the content in the drug solution preparation process, the integrity of the sterile filter in the sterile filtration process, the weight of the filled solution in the filling process, and confirmation of crimping in the crimping process.

2.A.(2).3) History of changes in the manufacturing process and comparability between pre-change and post-change drug product

The major change in the manufacturing process of the drug product in the course of development was the lyophilization cycle. The comparability of the drug product manufactured in the lyophilization cycle before the change (P1 product) and that manufactured in the lyophilization cycle after the change (P2 product) was assessed by the following tests. As a result of these tests, the applicant determined that these drug products were comparable. The P1 product contained the drug substance manufactured by the P1-ATO method, while the P2 product contained the drug substance manufactured by the P2-ATO and P2-ACO methods.

Purity (gel filtration HPLC, cation-exchange HPLC, reversed-phase HPLC),

electrophoretic pattern (SDS-PAGE), identification (ELISA), biological activity ([redacted]), description (visual observation), sterility (membrane filter method), endotoxins (bacterial endotoxins test), osmolarity (osmolarity determination), polysorbate 20 (spectroscopy), water content (Karl Fischer method), insoluble particulate matter (insoluble particulate matter test), protein concentration (HPLC), pH (pH determination), amino acid sequence (Lys-C mapping), methionine oxidation (Lys-C mapping), molecular weight (mass spectrometry, sedimentation velocity ultracentrifugation, gel filtration HPLC-static light scattering), secondary structure (circular dichroism [CD] spectrum [far ultraviolet], Fourier transform infrared spectroscopy), tertiary structure (CD spectrum [near ultraviolet], fluorescence spectrum), process-related impurities ([redacted]), thermo stability (differential scanning calorimetry), and stability (long-term testing, stress testing)

The pharmacokinetics and pharmacodynamics of the P1 and P2 products have been evaluated in 2 subgroups (Subsets A and B) in Foreign study 20030213 [see 4.(i) Summary of biopharmaceutics studies].

2.A.(2).4) Specifications

The proposed specifications (test methods) for the drug product include description (visual inspection), identification (ELISA), osmolarity (osmolarity determination), pH (pH determination), purity (gel filtration HPLC, cation-exchange HPLC, reversed-phase HPLC), water content (Karl Fischer method), endotoxins (bacterial endotoxins test), uniformity of dosage units (mass variation tests), foreign insoluble matter (foreign insoluble matter test), insoluble particulate matter (insoluble particulate matter test), sterility (membrane filter method), biological activity ([redacted]), polysorbate 20 (spectroscopy), and assay (HPLC).

2.A.(2).5) Stability of drug product

A long-term testing (5°C, 36 months), accelerated testing ([redacted]°C, [redacted] months), and stress testing ([redacted]°C, [redacted] months) were conducted using 3 batches of the P2 product manufactured at a pilot scale. In addition, photostability testing (white fluorescent lamp [1.2 million lx·h] + near ultraviolet fluorescent lamp [200 W·h/m^2], 5°C) was carried out using one batch. The tested items of the drug product include the description, water content, pH, purity, biological activity, assay, and electrophoretic pattern. In the long-term testing, insoluble particulate matter and the sterility of the drug product were also included in the test.

The drug substance was stable for 36 months without any change over time in any of these tests in the long-term testing. [redacted].

[redacted].

Based on the above stability test results, a shelf life of 36 months when stored at 5°C and protected from light has been proposed for the drug product.

Additionally, the drug product was dissolved in water for injection and subjected to stability testing under the storage conditions of rutine use (2000 lx, room temperature [25°C] or 5°C). [redacted]

[redacted]. Based on the above stability test results, the drug product after being dissolved in water for injection should be stored at room temperature or in a refrigerator (2°C-8°C) and protected from light; it should be injected within 24 hours.

2.A.(3) Reference materials

The primary reference material is prepared by dissolving the drug substance in a solution containing L-histidine, D-mannitol, sucrose, and polysorbate 20 at pH 5.0 so that the protein concentration in the solution is 0.5 mg/mL. It is then lyophilized according to the manufacturing process of the drug product and stored at [redacted]°C or below. A shelf life of [redacted] years has been proposed temporarily. The stability testing of the primary reference material is ongoing. The specifications (test methods) for the primary reference material include description (visual inspection), identification (ELISA), pH (pH determination), purity (gel filtration HPLC, cation-exchange HPLC, reversed-phase HPLC), water content (Karl Fischer method), biological activity ([redacted]), and assay (HPLC). If the primary reference material needs to be renewed, the compatibility of a newly prepared primary reference material should be confirmed according to the above specifications (test methods). No working reference material has been established.

2.B Outline of the review by PMDA

PMDA requested the applicant to add a peptide mapping, which has a high specificity to the desired product and detects minute structural changes accompanied by no change in electrical charge or hydrophobicity, to the specifications and tests of the drug substance or product in order to ensure the structural consistency of romiplostim.

The applicant responded as follows:
Upon obtaining necessary data for establishing such a peptide mapping for identification, the applicant will submit an application for a partial change in the approved specifications and test methods of the drug product to add identification (peptide mapping). Until obtaining an approval for this partial change, an in-process control using a peptide mapping will be performed in the manufacturing process of the drug product.

PMDA considers as follows:
To ensure the structural consistency of romiplostim in the drug product, it is necessary to add a peptide mapping to the specifications and test methods of the drug product. However, PMDA has accepted the applicant's proposal that the in-process control using a peptide mapping will be performed in the manufacturing process of the drug product as the second best policy at present to control the structural consistency of romiplostim in the drug product until an approval for the partial change is obtained.

Based on the submitted data, PMDA reviewed the quality of romiplostim and concluded that there are no particular problems with the quality of romiplostim.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Binding affinities of romiplostim and TPO for soluble recombinant human and mouse TPO receptors (Attached document 4.2.1.1-1, Reference data)

The binding affinities of romiplostim and recombinant human TPO (rhuTPO) for the soluble recombinant human and mouse TPO receptors (rhuMpl and rmuMpl, respectively) were determined by surface plasmon resonance (BIAcore 2000). The dissociation constant (K_D), association rate constant (ka), and dissociation rate constant (kd) for romiplostim binding to rhuMpl were 14 nmol/L, 5.72×10^6 $mol^{-1}Ls^{-1}$, and 8.13×10^{-2} s^{-1}, respectively; for romiplostim binding to rmuMpl were 3.5 nmol/L, 1.61×10^7 $mol^{-1}Ls^{-1}$, and 5.53×10^{-2} s^{-1}, respectively. The K_D, ka, and kd for rhuTPO binding to rhuMpl were 33 nmol/L, 7.6×10^5 $mol^{-1}Ls^{-1}$, and 2.49×10^{-2} s^{-1}, respectively; for rhuTPO binding to rmuMpl were 66 nmol/L, 5.0×10^5 $mol^{-1}Ls^{-1}$, and 3.26×10^{-2} s^{-1}, respectively.

3.(i).A.(1).2) Binding affinities of romiplostim, its deamidated isomer and oxidized isomer for rhuMpl (Attached document 4.2.1.1-2)

The binding affinities of romiplostim, its deamidated isomer and oxidized isomer for rhuMpl were determined by surface plasmon resonance (BIAcore 3000). The K_D of the respective compounds above to rhuMpl were 0.51, 0.66, and 0.65 nmol/L.

3.(i).A.(1).3) Binding affinities of romiplostim for platelets derived from different species (Attached document 4.2.1.1-3, Reference data)

The binding affinities of romiplostim and rhuTPO for platelets derived from humans, rats, and monkeys were determined based on the radioactivity bound to the platelets after they were exposed to romiplostim or rhuTPO at various concentrations and ^{125}I-labeled rhuTPO. The radioactivity bound to platelets of human or animal origins decreased as the concentration of romiplostim or rhuTPO increased. The concentration of romiplostim required to completely replace the binding of ^{125}I-labeled rhuTPO to platelets was higher than that of rhuTPO in all species.

3.(i).A.(1).4) Effects of megakaryocyte growth factor and romiplostim on the colony formation of megakaryocytes from CD34 positive cells derived from cynomolgus monkey bone marrow (Attached document 4.2.1.1-4)

Romiplostim 1, 3, 10, 30, 100, 300, or 1000 ng/mL, recombinant human megakaryocyte growth and development factor (rhuMGDF) 1, 3, 10, 30, 100, 300, or 1000 ng/mL, or the vehicle was added to CD34 positive cells derived from cynomolgus monkey bone marrow and incubated in the presence of stem cell factor (SCF) 100 ng/mL, interleukin-3 (IL-3) 100 ng/mL, or interleukin-6 (IL-6) 100 ng/mL for 14 days. The megakaryocytic colony-forming ability was determined based on the count of megakaryocyte colony-forming cells (MK-CFC). The MK-CFC count increased as the concentration of romiplostim or rhuMGDF increased. The 50% effective concentration (EC_{50}) was 2.06 or 0.18 nmol/L, respectively.

3.(i).A.(1).5) Effects of MGDF and romiplostim on the colony formation of megakaryocytes from CD34 positive cells derived from human peripheral blood (Attached document 4.2.1.1-5)

Romiplostim 1, 3, 10, 30, 100, 300, or 1000 ng/mL, rhuMGDF 1, 3, 10, 30, 100, 300, or 1000 ng/mL, or the vehicle was added to CD34 positive cells derived from human peripheral blood and incubated in the presence of SCF 100 ng/mL, IL-3 100 ng/mL, or IL-6 100 ng/mL for 14 days. The megakaryocytic colony-forming ability was determined based on the MK-CFC count. The MK-CFC count increased as the concentration of romiplostim or MGDF increased, and the EC_{50} was 1.14 or 0.52 nmol/L, respectively.

3.(i).A.(1).6) Platelet-increasing effect of a single intravenous or subcutaneous dose of romiplostim on mice (Attached document 4.2.1.1-6)

Female BDF_1 mice (9 weeks of age, n = 5/time point) received a single subcutaneous or intravenous dose of romiplostim 10, 30, 100, or 300 μg/kg, or a single subcutaneous dose of the vehicle. The platelet-increasing effect of romiplostim was evaluated based on the platelet count at baseline (only in the vehicle group) and up to 16 days after administration (3-10, 12, 14, 16 days after administration). The maximum platelet count (PLT_{max}) increased in a dose-dependent manner in both the administration routes. At any equal dose levels, the platelet counts were almost comparable between the 2 administration routes at all the time points. The time corresponding to the PLT_{max} (day of peak response) increased in a dose-dependent manner. The time to the day when the platelet count returned to the same level of that in the vehicle group after dosing increased in a dose-dependent manner.

3.(i).A.(1).7) Platelet-increasing effect of a single subcutaneous dose of romiplostim on mice (Attached document 4.2.1.1-7)

Female BDF_1 mice (9 weeks of age, n = 5/time point) received a single subcutaneous dose of romiplostim 0.1, 0.3, 1, 3, 5, 10, or 100 μg/kg or the vehicle. The platelet-increasing effect of romiplostim was evaluated based on the platelet count from the day of administration to 17 days after that (1-11, 13, and 17 days after administration at the doses other than 100 μg/kg; 1-9, 11, 13, and 17 days after that at 100 μg/kg). The PLT_{max} increased in a dose-dependent manner. In the ≥3 μg/kg groups, the platelet count increased more than twice that at the day of administration. Peak response was seen 5 days after administration at the doses other than 100 μg/kg and 6 days after that at 100 μg/kg.

3.(i).A.(1).8) Platelet-increasing effect of a single intravenous or subcutaneous dose of romiplostim on rats (Attached document 4.2.1.1-8)

Female CD rats (>10 weeks of age, n = 4/time point) received a single subcutaneous or intravenous dose of romiplostim 10, 30, 100, or 300 μg/kg or the vehicle. The platelet-increasing effect of romiplostim was evaluated based on the platelet count from the day before administration (only in the vehicle group) up to 22 days after that (3, 6, 9, 12, 14, and 22 days after adoministration). The platelet count was almost comparable between the 2 administration routes at the same doses at all of the time points. The PLT_{max} increased in a dose-dependent manner.

3.(i).A.(1).9) Platelet-increasing effect of a single subcutaneous dose of romiplostim on splenectomized mice (Attached document 4.2.1.1-9)

Splenectomized or non-splenectomised female BDF_1 mice (68 days of age in the splenectomy group, 47 days of age in the untreated group, n = 5/time point) received a single subcutaneous dose of romiplostim 10, 50, or 100 μg/kg, or the vehicle. The platelet count was measured from 1 to 15 days after administration. The ratios of the platelet counts in untreated and splenectomized animals receiving romiplostim to the mean platelet counts (1343×10^6 and 1532×10^6/mL, respectively) in those animals receiving vehicle during the evaluation period were determined. The platelet-increasing effect of romiplostim was evaluated based on these ratios. The PLT_{max} increased in a dose-dependent manner in either untreated or splenectomized mice.

3.(i).A.(1).10) Platelet-increasing effect of repeated subcutaneous doses of romiplostim on ITP mouse models (Attached document 4.2.1.1-10)

The platelet count in male W/BF_1 mice (n = 43) was measured once between 7 and 12 weeks of age (before the occurrence of thrombocytopenia) to determine the normal range of platelet count (1,332,000 ± 233,000/μL). Of these mice, those with decreased platelet count below normal range later at the age of 17 to 22 weeks were splenectomized. (a) Among animals having a platelet count that returned to the normal range at 1 week after splenectomy and decreased again by 38 weeks

of age (splenectomy responders) (n = 6), those that survived at 41 weeks of age (n = 4) received repeated subcutaneous doses of romiplostim 50 μg/kg once weekly for 5 weeks from 41 weeks of age. The platelet count was measured in these animals up to 51 weeks of age. (b) Animals having a platelet count not in the normal range at 1 week after splenectomy (splenectomy non-responders) (n = 8) received repeated subcutaneous doses of romiplostim 50 μg/kg once weekly from 19 weeks of age and subsequently 500 (if the platelet count was <1,000,000/μL after dosing of romiplostim at 50 μg/kg) or 1000 μg/kg (if the platelet count was <1,000,000/μL after dosing of romiplostim at 500 μg/kg) according to the platelet count. The platelet count was measured in these animals up to 51 weeks of age at maximum. The platelet count in splenectomy responders was at the lower limit of the normal range or above during romiplostim dosing. Four splenectomy non-responders died (2 animals at 21 weeks of age at 50 μg/kg, 1 animal at 30 weeks of age at 50 μg/kg, 1 animal at 41 weeks of age at 500 μg/kg) by the age of 41 weeks. The remaining 4 non-responders survived up until 47 weeks of age. The platelet count in these survivors 1 week after romiplostim dosing was at the lower limit of the normal range or above.

3.(i).A.(1).11) Platelet-increasing effect of a single subcutaneous dose of romiplostim on monkeys (Attached document 4.2.1.1-11)

Male cynomolgus monkeys (3.5-5.4 years of age, n = 3) and male rhesus monkeys (1.5-2.5 years of age, n = 3) received a single subcutaneous dose of romiplostim 1 mg/kg. The platelet-increasing effect of romiplostim was evaluated based on the platelet counts on 3 days before dosing, and 3, 5, 7, 9, 11, 14, 17, and 21 days after dosing. The mean platelet counts in cynomolgus monkeys and rhesus monkeys were 467 ± 21 and 479 ± 21 × 10^3/mm^3 at baseline, respectively, and peaked to 935 ± 153 and 849 ± 63 × 10^3/mm^3, respectively, 11 days after dosing. The platelet counts returned to the baseline level in cynomolgus monkeys 21 days after dosing and in rhesus monkeys 17 days after dosing. The counts of polymorphonuclear neutrophils and eosinophils increased from baseline and reached more than twice the baseline count, while those of lymphocytes and monocytes were half the baseline count.

3.(i).A.(1).12) Pharmacodynamic response of platelets to romiplostim in monkeys and rodents (Attached document 4.2.2.2-1 to 4.2.2.2-3, 4.2.2.7-2)

Male rhesus monkeys (n = 3) received a single intravenous or subcutaneous dose of romiplostim 500, 2000, or 5000 μg/kg. The platelet count was measured from baseline until 21 to 27 days after dosing. Additionally, male cynomolgus monkeys (2.6-4.7 years of age, n = 3) received a single intravenous dose of romiplostim 500 or 5000 μg/kg or a single subcutaneous dose of romiplostim 5000 μg/kg. The platelet count was measured from baseline until 29 days after dosing. Male C57BL/6J mice (20-30 g, n = 5/time point) received a single intravenous dose of romiplostim 30, 100, or 300 μg/kg. The platelet count was measured from baseline until 14 days after dosing. Male SD rats (250-350 g, n = 3-4) received a single intravenous or subcutaneous dose of romiplostim 30, 100, or 300 μg/kg. The platelet count was measured from baseline until 21 days after dosing. The pharmacodynamic response of platelets to romiplostim was compared among these animal species based on the ratio of PLT_{max} at each point relative to the baseline PLT (maximum amplification factor) and the day of peak response. The maximum amplification factor and the day of peak response were almost equivalent for subcutaneous and intravenous dosing at the same doses among SD rats, rhesus monkeys, and cynomolgus monkeys. The maximum amplification factor increased in a dose-dependent manner in all of the animal species. The effective dose of romiplostim was lower in rodents than in monkeys. The day of peak response was delayed in a dose-dependent manner in rodents, while no dose dependency was seen in monkeys.

3.(i).A.(1).13) Efficacy study following a single subcutaneous dose of romiplostim in rats for formulation comparison (Attached document 4.2.1.1-12)

Female SD rats (6-8 weeks of age, n = 10) received a single subcutaneous dose of the frozen

product of romiplostim (30 μg/kg) and the lyophilized product of romiplostim (30 μg/kg). The difference in platelet counts between the 2 formulations was not significant on the day before administration, or 4, 7, 8, 9, 10, 12, or 14 days after administration.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effects of romiplostim on platelet function and signaling (Attached document 4.2.1.2-4)

Human platelets were exposed to romiplostim 1, 10, or 100 ng/mL, polyethyleneglycol (PEG)-conjugated rhuMGDF (PEG-rhuMGDF) 100 ng/mL, Fc-Leptin 1000 ng/mL, TMP 100 ng/mL, or the vehicle. Then, platelet aggregation was induced with adenosine diphosphate (ADP) (0.1-20 μmol/L). The platelet aggregation promoting effect of each test substance was evaluated using an ADP concentration-human platelet aggregation rate curve. The ADP concentration-human platelet aggregation rate curve shifted toward the left as the concentration of romiplostim increased. Romiplostim promoted ADP-induced platelet aggregation at ≥10 ng/mL. PEG-rhuMGDF and TMP also promoted aggregation of human platelets, while Fc-Leptin did not.

The signaling by romiplostim was evaluated based on tyrosine phosphorylation of the TPO receptor and JAK2 of human platelets after exposure in the presence or absence of romiplostim 1 μg/mL. Romiplostim 1 μg/mL phosphorylated the tyrosine of the TPO receptor and JAK2 of human platelets.

3.(i).A.(2).2) Receptor binding study (Attached document 4.2.1.2-1)

The binding affinity of romiplostim for 63 types of receptor or ion channel was determined. Romiplostim 2.0 μmol/L inhibited by more than - 50% the binding of specific ligands to estrogen receptors. On the other hand, romiplostim up to 2.0 μmol/L did not inhibit by more than ± 50% the binding of specific ligands to any receptors or ion channels other than the estrogen receptors. The inhibition of the binding of specific ligands to estrogen receptors by romiplostim was not dose-dependent, indicating that the inhibition was due to the enhanced binding of nonspecific ligands to the other receptors and ion channels than the estrogen receptors. The above results suggest that romiplostim has hardly any binding affinity for the receptors and ion channels assessed in this study.

3.(i).A.(2).3) Receptor selectivity study (Attached document 4.2.1.2-2)

Romiplostim or human Fc was allowed to bind to a sensor chip on which anti-human Fc antibodies were immobilized. These sensor chips were subjected to surface plasmon resonance (BIAcore 3000) to determine the binding affinity of romiplostim for soluble recombinant EPO receptor (EPO-R), G-CSF receptor (G-CSF-R), recombinant human growth factor receptor (GH-R), recombinant human prolactin receptor (PRL-R) at 30, 100, or 300 nmol/L, and the vehicle. Romiplostim did not bind to the EPO-R, G-CSF-R, GH-R, or PRL-R.

3.(i).A.(2).4) Effects on TPO receptor mRNA-expressing hepatic cancer cell line Hep3B (Attached document 4.2.1.2-3)

[redacted]. [redacted] cells proliferated as the dose of romiplostim or rhuTPO increased, while Hep3B did not in the least proliferate .

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Cardiovascular effects following a single intravenous dose of romiplostim in cynomolgus monkeys (Attached document 4.2.1.3-1)

Male cynomolgus monkeys (2-3 years of age, n = 3) received a single intravenous dose of romiplostim 500, 1000, or 5000 μg/kg, or the vehicle and were subjected to measurement of electrocardiogram (ECG) parameters (RR, PR, QRS, and QT intervals), blood pressure (diastolic, systolic, mean), and body temperature up to 10 days after dosing in conscious, unrestrained conditions. In 1 animal in the romiplostim 500 μg/kg group, body temperature and heart rate transiently increased from 1 to 3 days after dosing. In the other romiplostim groups, there were no deviations from the physiological range of blood pressure, heart rate, or body temperature. ECG waveform, cardiac rhythm, and the ECG parameters were within the normal range in all of the romiplostim groups.

3.(i).A.(3).2) Central nervous effects following a single subcutaneous dose of romiplostim in rats (Attached document 4.2.1.3-2)

Male and female SD rats (7 weeks of age, n = 8/sex) received a single subcutaneous dose of romiplostim 10, 30, or 100 μg/kg, or the vehicle. Romiplostim did not affect general conditions, behavior, body temperature, physical function, or locomotor activity.

3.(i).A.(3).3) Respiratory effects of romiplostim in 13- and 26-week repeated subcutaneous dose toxicity studies in cynomolgus monkeys (Attached document 4.2.3.2-4)

Male and female cynomolgus monkeys (2.5-6 years of age, n = 3/sex) received repeated subcutaneous doses of romiplostim 500, 1000, or 5000 μg/kg, or the vehicle once weekly, and blood gas (oxygen partial pressure, carbon dioxide partial pressure) and respiratory rate were examined at baseline, and Days 1, 10, and 83. Romiplostim did not affect blood gas or respiratory rate.

3.(i).A.(4) Pharmacodynamic drug interactions

No data were submitted.

3.(i).B Outline of the review by PMDA

PMDA asked the applicant to explain whether or not romiplostim potentially reacts in the body in a different manner from TPO does.

The applicant explained as follows:

TPO is currently identified as the only one *in vivo* ligand for TPO receptor. The activation and signaling of the TPO receptor by TPO are mediated only through JAK2 (Kaushansky K. *J Clin Invest.* 2005;115:3339-47). The phenotype of TPO-deprived mice is almost identical to that of TPO receptor-deprived mice (Alexander WS. *Int J Biochem Cell Biol.* 1999;31:1027-1035). In summary, TPO is the only *in vivo* ligand for the TPO receptor and the TPO receptor is the only *in vivo* receptor of TPO. On the other hand, romiplostim binds to the TPO receptor competitively with endogenous TPO in the TPO binding domain existing in the extracellular domain of the TPO receptor [see 3.(i).A.(1).3) Binding affinity of romiplostim for platelets derived from different species]. This compound binds to the TPO receptor to transmit activation signals into cells with phosphorylation of the intracellular domain and JAK2 (Broudy VC and Lin NL. *Cytokine.* 2004;25:52-60). Romiplostim did not bind to any of the following receptors: EPO-R, G-CSF-R, GH-R, or PRL-R [see 3.(i).A.(2).3) Receptor selectivity study]. These findings indicate that romiplostim binds only to the TPO receptor *in vivo*. In addition, romiplostim, as with TPO, is assumed to be involved in the control of hematopoietic stem cells and to inhibit the differentiation of megakaryocytes and erythroid progenitor cells to erythroblasts.

PMDA asked the applicant to explain potential of romiplostim on the tumor cell proliferation

taking into account the expression of the TPO receptor, as well as about the effects of romiplostim on malignant tumors.

The applicant responded as follows:
TPO promotes cell growth of mouse liver epithelial cell line LEC-1, where the TPO receptor is functionally expressed, in a dose-dependent manner (Cardier JE et al. *Blood.* 1998;91(3):923-9). Additionally, TPO and romiplostim enhance growth of [redacted] cells in a dose-dependent manner [see 3.(i).A.(2).4) Effects on TPO receptor mRNA-expressing hepatic cancer cell line Hep3B]. Accordingly, the cell growth-promoting activity of romiplostim appears to depend on the TPO receptor expression on cells. As romiplostim specifically acts on the TPO receptor, the possible activity of romiplostim on the tumor cell proliferation is only growth signaling via the TPO receptor expressed on cells. Its mechanism of action is not different from that of TPO. Therefore, the possibility for romiplostim to promote cell proliferation via the TPO receptor cannot be ruled out when the TPO receptor is functionally expressed on malignant tumors. In hematological cell lines, TPO enhances the growth of TPO receptor-expressing acute myeloid leukemia (Corazza F et al. *Blood.* 2006;107:2525-30, Fontenay-R.M et al. *Leuk Res.* 1998;22:527-35). On megakaryocytic cells, erythroid cells, and monocytic cells, TPO receptor mRNA is expressed (Columbyova L et al. *Cancer Res.* 1995;55:3509-12). Accordingly, romiplostim might have a potential to promote cell growth via the TPO receptor in these cell lines. The clinical studies of romiplostim in ITP patients in and out of Japan demonstrated that the incidence of adverse events related to hematopoietic organ tumor or myelodysplastic syndrome (MDS) was similar between romiplostim and placebo treated patients. In a foreign clinical study in MDS patients, however, progression to acute myeloid leukemia (3 patients), a transient increase in blast cell count (4 patients), and chronic myelomonocytic leukemia (1 patient) were reported. The safety of romiplostim has not been established in MDS patients.

PMDA considers as follows:
As the primary pharmacodynamic data indicated the binding of romiplostim to the TPO receptor, the platelet-increasing effect of romiplostim in ITP patients can be expected from the results of the *in vitro* studies using human- and monkey-derived cells and the *in vivo* study using ITP mouse model.

On the other hand, the possibility for romiplostim to enhance the cell growth of malignant tumors via the TPO receptor cannot be excluded. It is, therefore, necessary to carefully monitor the long-term safety of romiplostim in clinical practice. As the pharmacological effects of romiplostim, as with endogenous TPO, are mediated by the TPO receptor, careful attention should be paid to adverse drug reactions due to TPO receptor-mediated cell growth or differentiation other than the original intent in clinical practice.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The concentrations of romiplostim in samples were measured by ELISA using polyclonal antibodies that bind to the TMP of romiplostim (lower limit of quantification ranges 0.270-1.77 ng/mL depending on studies).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration (Attached document 4.2.2.2-1 to 4.2.2.2-3)

Male rats received a single intravenous dose of romiplostim 30, 100, or 300 μg/kg. The area under serum romiplostim concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) and the maximum serum concentration (C_{max}) of romiplostim increased almost proportionally to the dose (n = 2/time point). The systemic clearance (CL) and steady-state distribution volume (V_{ss}) of romiplostim were 6.33 to 8.44 mL/h/kg and 114 to 139 mL/kg, respectively. Male rats received a single subcutaneous dose of romiplostim 30, 100, or 300 μg/kg. The serum concentration of romiplostim

reached C_{max} at 8 to 16 hours post-dose. The C_{max} and $AUC_{0-\infty}$ of romiplostim increased in a dose-dependent manner (n = 2/time point). The elimination half-life ($t_{1/2}$) following subcutaneous dose of romiplostim was 18.7 to 20.6 hours, which was nearly equivalent to the $t_{1/2}$ following intravenous dose of romiplostim (17.0-19.2 hours). The bioavailability (F) of romiplostim was 20.6% to 27.9%.

Male cynomolgus monkeys (n = 3) received a single intravenous dose of romiplostim 500 or 5000 μg/kg. The CL and V_{ss} of romiplostim were 17.3 to 20.1 mL/h/kg and 110 to 198 mL/kg, respectively. The F following a single subcutaneous dose of romiplostim 5000 μg/kg was 19.2%. The $t_{1/2}$ following subcutaneous dose of romiplostim was 296 hours, which was longer than the $t_{1/2}$ following intravenous dose of romiplostim (68.1-96.1 hours).

Male rhesus monkeys (n = 3) received a single intravenous dose of romiplostim 500, 2000, or 5000 μg/kg. The $AUC_{0-\infty}$ of romiplostim increased almost dose-proportionally. The CL and V_{ss} of romiplostim were 7.44 to 7.76 mL/h/kg and 184 to 196 mL/kg, respectively. Male rhesus monkeys (n = 3) received a single subcutaneous dose of romiplostim 500, 2000, or 5000 μg/kg. The serum concentration of romiplostim reached C_{max} at 4 to 8 hours post-dose. The F of romiplostim 500, 2000, and 5000 μg/kg were 73.7%, 47.7%, and 44.5%, respectively. The $t_{1/2}$ following a subcutaneous dose of romiplostim was 110 hours in the 500 μg/kg group, which was almost equivalent to that following intravenous dose of romiplostim, while it was 195 hours in the 5000 μg/kg group.

3.(ii).A.(1).2) Repeated-dose administration (Attached document 4.2.3.2-1 to 4.2.3.2-4)

Male and female rats received repeated subcutaneous doses of romiplostim 10, 30, or 100 μg/kg, or repeated intravenous doses of romiplostim 100 μg/kg 3 times weekly for 4 weeks. The serum concentration of romiplostim reached C_{max} at 12 hours after the initial dose at 30 and 100 μg/kg in the subcutaneous groups. As the dose increased from 30 to 100 μg/kg, the C_{max} and the area under serum romiplostim concentration-time curve from time 0 to 48 hours post-dose (AUC_{0-48}, the suffix representing the time after dosing) increased approximately 10 and 8 times (n = 6/time point), respectively. As the serum concentrations of romiplostim were not high enough for pharmacokinetic analysis in the 10 μg/kg group (lower limit of quantification, 1.21 ng/mL), the data were excluded from the analysis. The accumulation rate (AR) after repeated dose of romiplostim 3 times weekly for 4 weeks was 0.934 to 1.25 in the subcutaneous groups and 0.705 in the intravenous 100 μg/kg group.

Female cynomolgus monkeys (n = 6-8) received repeated subcutaneous doses of romiplostim 100, 300, 500, or 5000 μg/kg 3 times weekly for 4 weeks. The serum concentration of romiplostim reached C_{max} at 4 to 6 hours after the initial dose. The AUC_{0-24} increased almost dose-dependently. The AR of romiplostim was 0.437, 1.40, 2.04, or 2.11 at the respective doses above. Female rhesus monkeys (n = 7) received repeated subcutaneous doses of romiplostim 5000 μg/kg 3 times weekly for 4 weeks. The C_{max} and AUC_{0-24} were approximately twice those in cynomolgus monkeys.

Male and female rhesus monkeys (n = 6-10) received repeated subcutaneous doses of romiplostim 500, 1000, or 5000 μg/kg 3 times weekly for 4 weeks. The serum concentration of romiplostim reached C_{max} at 4 to 8 hours after the initial dose. When the dose increased from 500 to 5000 μg/kg, the AUC_{0-48} increased 6 to 7 times. The F of subcutaneous dose of romiplostim 5000 μg/kg relative to intravenous dose of romiplostim 5000 μg/kg was 28.2% after the initial dose. The AR of repeated subcutaneous doses of romiplostim was 1.81 to 2.14. Binding- and neutralizing-antibodies against romiplostim were produced after repeated dose of romiplostim. These antibodies did not affect the pharmacokinetics of romiplostim.

Male and female cynomolgus monkeys received repeated subcutaneous doses of romiplostim 500,

1000, or 5000 μg/kg once weekly for 26 weeks. The C_{max} and AUC_{0-24} increased almost in a dose-dependent manner. The AR of romiplostim calculated from the AUC_{0-24} at Weeks 13 and 26 was 1.05 to 1.65 (n = 15-16/time point, except for Week 26 [n = 9-10/time point]). Binding- and neutralizing-antibodies against romiplostim were produced after repeated dose of romiplostim. The romiplostim-binding antibody did not generally affect the pharmacokinetics of romiplostim. However, in 1 animal in which the production of the romiplostim-neutralizing antibodies was seen at Week 4, the serum concentration of romiplostim at Week 13 significantly decreased from that at Week 1, and the exposure to romiplostim decreased.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution (Attached document 4.2.2.3-1)

Female rats received a single intravenous dose of ^{125}I-labeled romiplostim 300 μg/kg. The radioactivity concentrations in tissues were measured at 0.5, 12, 72, and 168 hours post-dose (n = 2/time point). The radioactivity concentration reached the maximum at 0.5 or 12 hours post-dose in all of the tissues. The radioactivity concentration was highest in serum, except in the thyroid, followed by in blood, cellular fraction, the kidneys, bone marrow, liver, spleen, adrenals, and ovaries. The radioactivity was widely distributed in the other tissues as well. In all of the tissues, the radioactivity was still detected at 168 hours post-dose, and it was highest in serum and lowest in the brain. The radioactivity concentration in trichloroacetic acid (TCA) insoluble fraction was 83.6% to 94.8% of the total radioactivity, suggesting that most of the radioactivity existing in the tissues assessed (serum, spleen, kidneys, liver, heart, ovaries) was unchanged romiplostim or a polymeric fraction of romiplostim.

The radioactivity distribution determined by a quantitative autoradiogram after a single intravenous dose of ^{125}I-labeled romiplostim 300 μg/kg to female rats was generally consistent with the tissue concentration data. The radioactivity concentration remaining at 168 hours post-dose was highest in kidneys, followed by in blood, renal medulla, thyroid, lungs, and adrenals. The radioactivity concentration was below the lower limit of quantification (3.61 ng equivalent to ^{125}I-labeled romiplostim/g or mL) in cerebellum, cerebrum, medulla, olfactory lobe, spinal cord, and gastric contents.

3.(ii).A.(2).2) Fetal distribution (Attached document 4.2.3.5.2-1)

Pregnant rats received repeated subcutaneous doses of romiplostim 10, 30, or 100 μg/kg on Gestation days 7, 9, 11, 13, 15, 17, and 19. The AR of romiplostim in maternal serum on Gestation day 19 relative to Gestation day 7 was 0.373, 0.761, or 0.510, at respective doses above (n = 3/time point). The romiplostim concentration in fetal serum on Gestation day 19 was approximately 50% of that in maternal serum, suggesting that romiplostim crossed the placenta. The AUC_{0-48} and C_{max} of romiplostim in maternal and fetal serum increased more than dose-proportionally. The individual difference in romiplostim concentrations over time in amniotic fluid was large. The C_{max} of romiplostim in amniotic fluid was 11% to 44% of that in maternal serum on Gestation day 19.

3.(ii).A.(3) Metabolism (Attached document 4.2.2.4-1)

Male and female rats received a single intravenous dose of ^{125}I-labeled romiplostim 300 μg/kg. The serum romiplostim concentrations were measured by the conventional ELISA (using polyclonal antibodies that recognize TMP) and ELISA for metabolism studies (using polyclonal antibodies that recognize TMP and human Fc domain) (n = 2/time point). The serum romiplostim concentrations over time determined by the conventional ELISA were lower than those determined by the ELISA for metabolism studies (Figure 1), suggesting the presence of a metabolite with at least 1 of the 2 TMP chains lost in serum. In addition, the difference in serum romiplostim concentration between the 2 types of ELISA became larger over time, indicating that the TMP chain of romiplostim is cleaved over time in circulating blood.

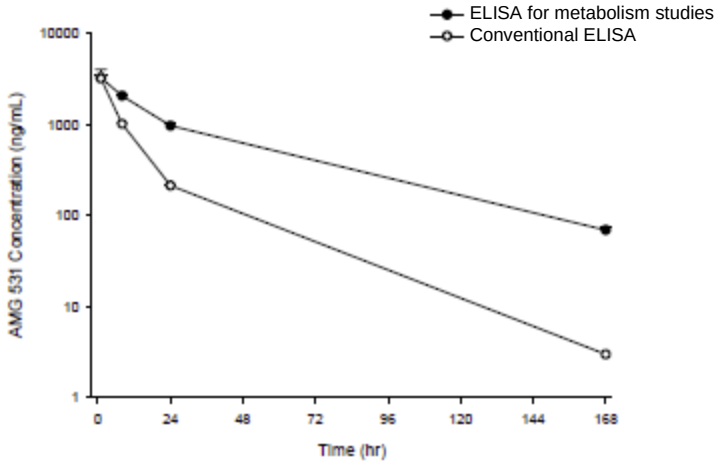


Figure 1. Comparison of serum romiplostim concentrations over time in rats given a single intravenous dose of ^{125}I-labeled romiplostim measured by two types of ELISA
(mean, n = 2; Study Number 102253) (partially modified from the submitted data)

As romiplostim is a recombinant protein consisting of only amino acids, to which "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PMSB/ELD Notification No. 326 dated February 22, 2000) is applicable, no *in vitro* metabolism studies have been conducted in consideration of this notification.

3.(ii).A.(4) Excretion (Attached document 4.2.2.3-1)

Female rats received a single intravenous dose of ^{125}I-labeled romiplostim 300 μg/kg. Up to 24 hours post-dose, 51.3% and 2.63% of the administered radioactivity were excreted in urine and feces (n = 3/time point), respectively. Up to 168 hours post-dose, 87.7% and 6.56% of the radioactivity were excreted in urine and feces, respectively. The percentage of the TCA insoluble fraction relative to the total radioactivity in urine and feces was 10.7% to 11.3% and 45.9% to 49.2%, respectively, indicating that most of the recovered radioactivity was free ^{125}I or peptide fraction.

3.(ii).A.(5) Other pharmacokinetic studies

3.(ii).A.(5).1) Comparison of serum concentrations over time between romiplostim formulations in rats (Attached document 4.2.2.7-1)

Male rats received a single subcutaneous dose of the frozen product of romiplostim (30 μg/kg) or the lyophilized product of romiplostim (30 μg/kg). The means of C_{max} of romiplostim were 6.04 and 6.12 ng/mL for the respective 2 formulations above; the means of t_{max}, 24 and 12 hours, respectively; the means of $AUC_{0-\infty}$, 316 and 285 ng·h/mL, respectively; and the means of $t_{1/2}$, 25.5 and 27.6 hours, respectively, (n = 8/time point).

3.(ii).A.(5).2) Serum concentrations over time of intravenous dose of romiplostim in mice (Attached document 4.2.2.7-2)

Male mice received a single intravenous dose of romiplostim 30, 100, or 300 μg/kg. As the dose of romiplostim increased, the CL of romiplostim decreased from 43.3 to 11.5 mL/h/kg and the V_{ss} of romiplostim from 161 to 87.4 mL/kg. The AUC of romiplostim increased from 577 to 26,100 ng·h/mL. The $t_{1/2}$ of romiplostim was prolonged from 6.14 to 15.0 hours (n = 5/time point for all of the parameters).

3.(ii).A.(5).3) Serum concentrations over time of romiplostim in thrombocytopenic mice (Attached document 4.2.2.7-3, 4)

Mice received an intraperitoneal dose of carboplatin 62.5 mg/kg, followed by total body X-ray

irradiation of 5 Gy at 1 hour post-dose, to induce thrombocytopenia. At 11 days after irradiation, the thrombocytopenic mice (n = 5/time point) received a single intravenous dose of romiplostim 3 or 30 μg/kg. The C_{max} of romiplostim was 13.5 or 175 ng/mL at these respective doses. The AUC was 90.7 ($AUC_{0-\infty}$) or 1010 ng·h/mL (AUC_{0-24}), respectively. On the other hand, after a single intravenous dose of romiplostim 3 μg/kg to normal mice (n = 5/time point), the romiplostim concentrations in plasma were below the lower limit of quantification at almost all of the time points. The C_{max} and AUC_{0-24} of romiplostim after single intravenous dosing of 30 μg/kg to normal mice were 178 ng/mL and 1250 ng·h/mL, respectively, which were equivalent to those in thrombocytopenic mice.

3.(ii).A.(5).4) Serum concentrations over time of romiplostim in fetal Fc receptor knockout mice (Reference data 4.2.2.7-5)

Male fetal Fc receptor (Fc-Rn) knockout mice (n = 3/time point) and male wild-type mice (n = 3/time point) received a single intravenous dose of romiplostim 100 or 1000 μg/kg. The serum romiplostim concentrations over time in knockout mice were lower than those in wild-type mice. Romiplostim was detected in serum of wild-type mice at 24 and 96 hours post-dose, while in the knockout mice, the serum romiplostim concentrations at 10 and 20 hours post-dose were already below the lower limit of quantification (1.77 ng/mL).

3.(ii).A.(5).5) Serum concentrations over time of romiplostim in splenectomized rats (Attached document 4.2.2.7-6)

Male splenectomized rats (n = 3/time point), male non-splenectomized rats (n = 3/time point), and male sham rats (n = 3/time point) received a single intravenous dose of romiplostim 100 or 1000 μg/kg. The $AUC_{0-\infty}$ of romiplostim was 16,100 or 99,900 ng·h/mL at the respective doses above in the splenectomy group; 10,700 or 101,000 ng·h/mL, respectively, in the untreated group; and 11,100 or 132,000 ng·h/mL, respectively, in the sham group. There were no significant differences in the CL, V_{ss}, or $t_{1/2}$ of romiplostim among the groups.

3.(ii).A.(5).6) Serum concentrations over time of romiplostim in nephrectomized rats (Attached document 4.2.2.7-7)

Male bilaterally nephrectomized rats (n = 4/time point), male non-nephrectomized rats (n = 4/time point), and male sham rats (n = 4/time point) received a single intravenous dose of romiplostim 30 or 300 μg/kg. The AUC of romiplostim in the nephrectomy group was higher than that in the sham group by 26% or 80% at the respective doses above.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Biological activity of metabolite

Considering the applicant's explanation that romiplostim is suggested to have a metabolite with at least 1 TMP chain lost, which remains in serum for longer time than unchanged romiplostim, PMDA asked the applicant to explain the necessity of discussing the biological activity of this metabolite.

The applicant responded as follows:
The difference in concentrations over time between romiplostim and the metabolite determined by the 2 types of ELISA became larger over time, suggesting that romiplostim was eliminated from serum through clearance mediated by receptors expressed on the surface of platelets etc. On the other hand, as the metabolite has a decreased binding affinity for receptors due to the loss of a peptide chain(s), the same mechanism as that of romiplostim does not operate in its elimination. Thus the elimination half-life of the metabolite is longer than that of unchanged romiplostim. The molecular weight of romiplostim is approximately 59,000, while that of the metabolite is approximately 55,000. As the difference in molecular weight is small, the behaviors of these compounds as polymers are similar. Therefore, the effects of the receptor-mediated clearance appear to have resulted in the difference between the compounds in their concentrations over time.

The metabolite with 1 TMP chain lost is unlikely to bind to receptors and is expected to have no biological activity.

In *in vivo* study of administration of romiplostim, the efficacy of the metabolite with 1 TMP chain lost as well as unchanged romiplostim was evaluated. Following a single intravenous dose of ^{125}I-labeled romiplostim 300 μg/kg to normal rats, the serum concentration of the metabolite was approximately 20 times that of unchanged romiplostim at 7 days post-dose. The platelet count after single intravenous dose of romiplostim at the same dose peaked on Day 9 in normal rats, then decreased until Day 14, and returned to the baseline level on Day 22. This platelet response was not markedly prolonged compared with that after single intravenous dose of romiplostim 100 μg/kg, which was conducted simultaneously, suggesting a limited contribution of the metabolite remaining in serum to the efficacy of romiplostim. In the mouse *in vivo* experiment, romiplostim and double-chain FcTMP (1 TMP binding to each Fc domain) increased platelet count, but the pharmacological activity of FcTMP was weaker than that of romiplostim. On the other hand, neither TMP nor TMP-TMP chain alone showed any pharmacological activity. The above findings suggested that the metabolite with 1 TMP chain lost has significantly weaker pharmacological activity than that of romiplostim, or has no such activity.

Based on the above, as the metabolite with 1 TMP chain lost is unlikely to be biologically active, the pharmacological activity of this metabolite was not investigated.

Considering the applicant's explanation that the data suggest no or weak pharmacological activity of the metabolite with 1 TMP chain lost, PMDA concluded that prolonged retention of the metabolite with at least 1 TMP chain lost in rat serum is unlikely to cause any clinically significant problem.

3.(ii).B.(2) Contribution of kidneys to excretion of romiplostim

Considering that the contribution of the kidneys to excretion of romiplostim is suggested and that the pharmacokinetics of romiplostim in patients with renal impairment has not been evaluated, PMDA asked the applicant to discuss the necessity to alert physicians to the use of romiplostim in patients with renal impairment.

The applicant explained as follows:

Following intravenous dose of ^{125}I-labeled romiplostim in rats, the cumulative excretion of radioactivity in urine up to 168 hours post-dose was 87.7%. The percentage of the TCA insoluble fraction, which is considered to represent the status of the polymer, was 10.7% to 11.3% of the administered radioactivity, indicating that most of the radioactivity excreted in urine was free ^{125}I detached from the labeled protein or a low molecular weight peptide, etc., partially cleaved from romiplostim. The percentage of ^{125}I-labeled romiplostim excreted in urine is thus likely to be low. The AUC of romiplostim after intravenous dosing of romiplostim 30 or 300 μg/kg to bilaterally nephrectomized rats was by 26% or 80% higher, respectively, than that in the sham group, indicating that the exposure to romiplostim was changed after nephrectomy in a dose-dependent manner. In the elimination of romiplostim from serum, saturable CL mediated by receptors expressed on platelets is assumed to be involved. The results from the study in bilaterally nephrectomized rats indicate that the contribution of renal excretion increases at high doses of romiplostim. However, the maximum clinical dose of romiplostim is 10 μg/kg, which is lower than the doses assessed in the nonclinical studies. Thus, the renal excretion of romiplostim appears to minimally contribute to the elimination of romiplostim from the human body. Accordingly, the exposure to romiplostim at the clinical dose is unlikely to change significantly in patients with renal impairment.

Based on the above, although the possibility for renal impairment to affect the exposure to romiplostim cannot be ruled out, changes in the pharmacokinetics of romiplostim in patients with

renal impairment is estimated to be negligible at the clinical dose, and it is unnecessary to alert physicians to the use of romiplostim in patients with renal impairment.

PMDA considers as follows:
Although the applicant explained that the contribution of renal excretion is negligible at the clinical dose, the plasma romiplostim concentrations in thrombocytopenic patients, i.e., the target patient population of romiplostim, are higher than those in healthy adult subjects, and therefore CL mediated by receptors expressed on platelets can be saturated at lower doses than the clinical dose. It cannot be concluded that the contribution of renal excretion is negligible. In addition, the applicant explained that a low molecular weight peptide etc., partially cleaved from romiplostim accounted for the majority in urine excretion. However, taking into account that serum metabolite concentrations over time in human are unknown and that there is no clinical experience with romiplostim in patients with renal impairment, it is necessary to provide an adequate caution. A final decision will be made, taking account of comments raised in the Expert Discussion.

3.(iii) Summary of the toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of romiplostim conducted include single-dose toxicity, repeat-dose toxicity, reproductive and developmental toxicity, immunogenicity, and formulation comparison studies.

3.(iii).A.(1) Single-dose toxicity studies (Attached document 4.2.3.1-1, 4.2.1.3-1)

As single-dose toxicity studies, subcutaneous dose toxicity study in SD rats (4.2.3.1-1) and intravenous dose cardiovascular toxicity study in male cynomolgus monkeys (4.2.1.3-1, Safety pharmacology study) were conducted. The approximate lethal dose was determined to be >1000 μg/kg in rats and >5000 μg/kg in cynomolgus monkeys. After dosing of romiplostim, platelet count increased in both animal species, which can be explained by its pharmacological action. The changes observed in rats included changes in erythrocytic parameters (decreases in red blood cell count, hemoglobin level, and hematocrit; increased mean platelet volume; increased mean corpuscular hemoglobin level), increased spleen weight, and extramedullary hemopoiesis in the spleen. In cynomolgus monkeys, the mean corpuscular volume tended to be low.

3.(iii).A.(2) Repeat-dose toxicity studies (Attached document 4.2.3.2-1, 4.2.3.2-2, 4.2.3.2-3, 4.2.3.2-4)

As repeat-dose toxicity studies, subcutaneous or intravenous dose toxicity studies in SD rats (4-week study), rhesus monkeys (4-week study), female cynomolgus monkeys and rhesus monkeys (4-week study), and cynomolgus monkeys (13- and 26-week studies) were conducted. In all of the studies, platelet count increased in the romiplostim groups due to the pharmacological action of romiplostim. In addition, changes considered to be related to the pharmacological action were also observed including changes in erythrocytic parameters (decreases in red blood cell count, hemoglobin level, and hematocrit; increase [only in rats] or decrease [only in monkeys] in mean platelet volume; and decrease or increase in reticulocyte count), increased spleen weight, extramedullary hemopoiesis in the spleen, and increased megakaryocyte count in bone marrow. Additionally, hematology revealed increased white blood cell count etc., due to increases in neutrophils and eosinophils (only in rats), monocytes (only in rats and rhesus monkeys), and lymphocytes. In rats, femoral and sternal hyperostosis or bone marrow fibrosis was noted, which was reversible after a recovery period.

Binding- and neutralizing-antibodies against romiplostim were produced in all of the animal species. Rats producing romiplostim-neutralizing antibodies showed an attenuated pharmacological response to romiplostim (platelet-increasing effect). In 1 cynomolgus monkey (26-week study), TPO-binding antibodies were produced but no TPO-neutralizing antibodies were detected.

The AUC in cynomolgus monkeys (26-week study) and rhesus monkeys (28-day study) after administration of romiplostim at the no observed adverse effect level (NOAEL, 5000 μg/kg) (20,100 and 66,300 ng·h/mL, respectively) was 705.3 to 4769.8 times the AUC in humans after subcutaneous dosing of romiplostim 5 to 7 μg/kg (13.9-28.5 ng·h/mL). The NOAEL for rats was determined to be ≤ the lowest dose level assessed.

3.(iii).A.(2).1) Four-week repeated subcutaneous and intravenous dose toxicity study in rats (Attached document 4.2.3.2-1)

Male and female SD rats (n = 10-15/sex) received repeated subcutaneous doses of romiplostim 0 (vehicle), 10, 30, or 100 μg/kg, or repeated intravenous doses of romiplostim 100 μg/kg 3 times weekly for 4 weeks. Among all the romiplostim groups, 13 deaths considered to be associated with romiplostim (5 animals in the study group, 8 animals in the satellite group [n = 32/sex/group]) occurred between Days 10 and 30. In the ≥10 μg/kg groups, reduced body weight gain (male), changes in erythrocytic parameters, enhanced platelet aggregation, and megakaryocytic hyperplasia in bone marrow were observed. The following changes were also observed in the study; megakaryocytic hyperplasia in the spleen, megakaryocytic infiltration in the liver, increased intravascular eosinophilic substances, and femoral bone marrow fibrosis in females in the ≥10 μg/kg groups and males in the ≥30 μg/kg groups; increased white blood cell count, increased spleen weight, decreased lymphocyte count in the spleen, extramedullary hemopoiesis in the liver, megakaryocytic infiltration in the lungs, and femoral hyperostosis in the ≥30 μg/kg groups; and increased plasma fibrinogen level, large spleen, enhanced extramedullary hemopoiesis in the spleen, and sternal hyperostosis in the 100 μg/kg group. The changes at the injection site noted in romiplostim groups included chronic dermal inflammation, epidermic necrosis, mononuclear cell infiltration into the muscular layer, regeneration image of muscle fibers, and subcutaneous mononuclear cell infiltration. These findings resolved after the 4-week recovery period, except for the increased spleen weight.

From the above results, the NOAEL was determined to be <10 μg/kg/dose (30 μg/kg/week).

3.(iii).A.(2).2) Four-week repeated subcutaneous and intravenous dose toxicity study in rhesus monkeys (Attached document 4.2.3.2-2)

Male and female rhesus monkeys (n = 3-5/sex) received repeated subcutaneous doses of romiplostim 0, 500, 1000, or 5000 μg/kg, or repeated intravenous doses of romiplostim 0 or 5000 μg/kg 3 times weekly for 4 weeks. The following changes were observed after subcutaneous dosing; changes in hematological parameters, large platelets, enhanced platelet aggregation, and megakaryocytic hyperplasia in the bone marrow in the ≥500 μg/kg groups; nucleated erythrocytes in males in the ≥500 μg/kg groups and females in the ≥1000 μg/kg groups; large ovaries, cystic graafian follicles, and multiple graafian follicles in females (accompanied by increases in estradiol, follicle-stimulating hormone and/or corpus luteum hormone levels) in the ≥1000 μg/kg groups; and increased spleen weight, decreased thymus gland weight accompanied by decreased thymus lymphocyte count, and erythroid hypoplasia due to decreased erythroid precursor cell count in the 5000 μg/kg group. In the intravenous 5000 μg/kg group, increased fibrinogen level, tendency of increased lactate dehydrogenase (LDH) level, and decreased thymus weight accompanied by decreased thymus lymphocyte count were noted. The changes at the subcutaneous injection site included perivascular mononuclear cell infiltration and inflammatory changes. These findings resolved or tended to resolve after the 4-week recovery period except for perivascular mononuclear cell infiltration at the injection site.

The changes reported in the study were considered to be due to the pharmacological action of romiplostim. The NOAEL was determined to be ≥5000 μg/kg/dose (15,000 μg/kg/week).

3.(iii).A.(2).3) Four-week repeated subcutaneous dose toxicity study in female cynomolgus monkeys and rhesus monkeys (Attached document 4.2.3.2-3)

Female cynomolgus monkeys (n = 6-8) received repeated subcutaneous doses of romiplostim 0, 100, 300, 500, or 5000 μg/kg, and female rhesus monkeys (n = 8) received repeated subcutaneous doses of romiplostim 0 or 5000 μg/kg 3 times weekly for 4 weeks. The changes observed in cynomolgus monkeys included megakaryocytic hyperplasia in the bone marrow in the ≥100 μg/kg groups, increased reticulocyte count and decreased bone marrow cell count in the ≥500 μg/kg groups, and increased white blood cell count, prolonged prothrombin time (PT), increased LDH, increased β_2-microglobulin as revealed by urinalysis, megakaryocytic infiltration and increased intravascular eosinophilic substances in the lungs, and extramedullary hemopoiesis in the submandibular lymph node in the 5000 μg/kg group. These findings were also observed in rhesus monkeys. In addition, prolonged activated partial thromboplastin time, increased creatinine phosphokinase (CPK), increased N-acetyl-β-D-glucosaminidase (NAG) as revealed by urinalysis, and increased progesterone and tendency of increased estradiol as detected by hormonal tests were observed in rhesus monkeys. In cynomolgus monkeys, imbalance in size between the right and left ovaries was seen in 1 animal each in the 100 and 300 μg/kg groups. In 1 animal in the 100 μg/kg group, increased weight and teratoma were observed in the left ovary. The changes at the injection site included hemorrhage, inflammatory cell infiltration, and mononuclear cell infiltration. These findings resolved or tended to resolve after the 4-week recovery period except for perivascular mononuclear cell infiltration at the injection site.

The increased hematopoietic parameters reported in the study were considered to be due to the pharmacological action of romiplostim. The NOAEL was determined to be 500 μg/kg/dose (1500 μg/kg/week) in cynomolgus monkeys.

3.(iii).A.(2).4) Thirteen- and 26-week repeated subcutaneous dose toxicity study in cynomolgus monkeys (Attached document 4.2.3.2-4)

Male and female cynomolgus monkeys (n = 8/sex up to Week 13, n = 5/sex up to Week 26) received repeated subcutaneous doses of romiplostim 0, 500, 1000, or 5000 μg/kg once weekly for 13 or 26 weeks. The changes seen in this study included decreased mean platelet volume in females in the 500 and 5000 μg/kg groups, changes in platelet morphology including massive platelets and megathrombocytes in the ≥500 μg/kg groups, increased white blood cell count (males) and megakaryocytic infiltration in the submandibular lymph node in the ≥1000 μg/kg groups. In the romiplostim groups, perivascular mononuclear cell infiltration was noted at the injection site.

These findings resolved or tended to resolve after the 8-week recovery period except for perivascular mononuclear cell infiltration at the injection site.

The changes reported in the study were considered to be due to the pharmacological action of romiplostim. The NOAEL was determined to be >5000 μg/kg/dose (5000 μg/kg/week).

3.(iii).A.(3) Genotoxicity study

As romiplostim is a recombinant protein, which is produced in *E. coli*, has a human IgG1 Fc domain and a TPO receptor-binding domain, and consists of only amino acids, the compound is unlikely to directly act on either DNA or chromosomal components. Accordingly, no genotoxicity study has been conducted.

3.(iii).A.(4) Carcinogenicity study

Since neutralizing antibodies were produced in rodents and continued stimulation of the TPO receptor was difficult, a long-term repeat-dose study will not provide any additional safety information. Accordingly, no carcinogenicity study has been conducted in rodents.

The applicant discussed the potentials for romiplostim to induce tumors and promote the growth of existing tumors as follows:
Hepatic cancer cell line Hep3B, one of the human solid cancer cell lines, has been confirmed to express mRNA of the TPO receptor (Columbyova L et al. *Cancer Res*. 1995;55:3509-12). Neither TPO nor romiplostim, however, stimulated the growth of Hep3B cells *in vitro* [see 3.(i).A.(2).4) Effects on TPO receptor mRNA-expressing hepatic cancer cell line Hep3B], indicating that the mRNA of the TPO receptor expressed on Hep3B does not function. In the 26-week repeat-dose toxicity study in cynomolgus monkeys, stimulation of the TPO receptor resulted in megakaryocytic hyperplasia in bone marrow but no hyperplastic lesion was seen in the other organs. Considering these findings, romiplostim is unlikely to induce tumors in normal tissues during long-term repeated administration. TPO promotes the growth of acute myeloid leukemia cells *in vitro*; however, no adverse events suggesting such a promoting action have been reported in the clinical studies.

3.(iii).A.(5) Reproductive and developmental toxicity studies

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (Attached document 4.2.3.5.1-1)

Male and female SD rats (n = 25/sex) received repeated subcutaneous doses of romiplostim 0, 10, 30, or 100 μg/kg 3 times weekly from 4 weeks before mating until the day before necropsy for male animals or from 2 weeks before mating until the day before necropsy (Gestation days 14-16) for female animals. One male and 1 female each in all of the romiplostim groups including the satellite groups died or were sacrificed moribund during the dosing period. The changes observed in animals that were sacrificed moribund in the 30 μg/kg group included stooping position, strabismus, coarse fur, eye and nasal discharges, and marked weight loss. The female deaths were likely induced by blood sampling before mating. In males and females, increased platelet count, large spleen, and production of binding- and neutralizing-antibodies against romiplostim were observed. There were decreases in body weight, body weight gain, and food intake in male rats in the ≥30 μg/kg groups; and decreases in food consumption and body weight gain from 4 to 8 days before mating in female rats in the 30 μg/kg group. However, no effects on fertility or embryonic development were found. From the above results, the NOAEL was determined to be 10 μg/kg/dose (30 μg/kg/week) for general toxicity in parental animals and >100 μg/kg/dose (>300 μg/kg/week) for fertility and early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development study in rats (Attached document 4.2.3.5.2-2)

Pregnant SD rats (n = 25 each) received alternate-day subcutaneous doses of romiplostim 0, 10, 30, or 100 μg/kg during Gestation days 7 to 19. No effects of romiplostim on maternal animal or fetus, other than the large spleen in the ≥30 μg/kg groups, were noted. The NOAEL was determined to be >100 μg/kg/dose (>300 or 400 μg/kg/week) for both maternal general and reproductive toxicity and embryo-fetal development.

The dose-finding part (4.2.3.5.2-1) of this study demonstrated maternal-fetal transfer of romiplostim.

3.(iii).A.(5).3) Embryo-fetal development study in mice (Attached document 4.2.3.5.2-3)

Pregnant CD1 mice (n = 8 each) received repeated subcutaneous doses of romiplostim 0, 3, 10, 30, or 100 μg/kg 3 times weekly during Gestation days 6 to 15. Reduced body weight gain was noted in the 100 μg/kg group and a large spleen and yellow brown area in the liver were observed in 1 animal in the group. In the 3 and 100 μg/kg groups, the incidence of post-implantation loss tended to be high, and fetal resorption occurred at a high frequency. The mean number of live fetuses per litter was low in the 100 μg/kg group. One fetal death occurred in the 3 μg/kg group, while no death was seen in the other groups. From the above results, the NOAEL was determined

to be 30 μg/kg/dose (90 μg/kg/week) for both maternal general and reproductive toxicity and embryo-fetal development.

3.(iii).A.(5).4) Embryo-fetal development study in rabbits (dose-finding study) (Attached document 4.2.3.5.2-4)

Pregnant NZW rabbits (n = 5 each) received alternate-day subcutaneous doses of romiplostim 0, 10, 30, 60, or 100 μg/kg during Gestation days 7 to 19. In the 100 μg/kg group, decreased food consumption and reduced body weight gain were noted. The external examination of fetuses detected malformations (cutaneous aplasia, ectrodactyly, gastroschisis) in 1 animal in the 100 μg/kg. As these changes occurred only in 1 animal, they were considered accidental. Rabbits were considered inappropriate for toxicity assessment of romiplostim because platelet-increasing effect of romiplostim was seen only slightly in this animal species. Accordingly, no embryo-fetal development study in rabbits has been conducted.

3.(iii).A.(5).5) Study for effects on pre- and postnatal development, and maternal function in rats (Attached document 4.2.3.5.3-1)

Pregnant SD rats (n = 44 each) received alternate-day subcutaneous doses of romiplostim 0, 10, 30, or 100 μg/kg from Gestation day 6 to Lactation day 20 or 21. The administration was started with 24 animals for each group. The numbers of animals tested positive or negative for neutralizing antibodies against romiplostim were determined. At 13 weeks later, in order to have 16 to 20 animals each with and without neutralizing antibodies included in each group, 20 animals were added to each group and subjected to the same experiment. Three dams in the 30 μg/kg group and 1 dam in the 100 μg/kg, which were tested negative for neutralizing antibodies, died after blood sampling during the terminal stage of lactation. The gestation period was slightly prolonged in the animals treated with romiplostim. The changes seen in animals negative for neutralizing antibodies included transient reduced body weight gain in the ≥10 μg/kg groups; the large spleen in the ≥30 μg/kg groups; and reduced body weight gain and decreased food consumption during lactation, total resorption of litter (3 of 14 animals), a decreased mean number of live offspring and a increased number of dead offspring per litter, and decreased survival on Lactation day 4 in the 100 μg/kg group. These changes were less severe or not observed in animals tested positive for neutralizing antibodies.

From the above results, the NOAEL was determined to be 30 μg/kg/dose (90 or 120 μg/kg/week) for maternal general toxicity, 100 μg/kg/dosing (300 or 400 μg/kg/week) for maternal function, and 30 μg/kg/dose (90 or 120 μg/kg/week) for F_1 offspring.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Local tolerance

No local tolerance study has been conducted. In the repeated subcutaneous and intravenous dose toxicity studies, chronic inflammatory changes were noted at the injection site, which might be immunological responses to injection of a heterogeneous protein. However, no findings suggested the potential for romiplostim to damage cells and thereby cause local irritant effects.

3.(iii).A.(6).2) Immunogenicity (Attached document 4.2.3.7.1-1)

Female BD-F1 mice received a single subcutaneous dose of romiplostim 50 μg/kg to determine platelet count and antibody production every day up to 21 days after dosing. Binding antibodies against TMP were produced from 1 day after dosing; against Fc domain, from 6 days after dosing; and against romiplostim, from 11 days after dosing. TPO-binding antibodies were detected on 9, 10, and 21 days after dosing. Female BD-F1 mice received repeated subcutaneous doses of romiplostim 100 μg/kg 4 times every 21 days. Binding antibodies against TMP, romiplostim, and Fc domain were produced, while no binding antibodies against PEG-rhuMGDF were detected. After repeated subcutaneous dose of romiplostim 50 μg/kg 4 times every 21 days, binding

antibodies against TMP and romiplostim were produced, but TPO-binding antibodies were not. Furthermore, 21 days after a single subcutaneous dose of romiplostim 50 μg/kg, repeated subcutaneous doses of romiplostim 50, 100, 500, or 1000 μg/kg 6 times every 21 days were given. The binding antibodies against TMP and romiplostim were produced, while no TPO-binding antibodies were detected. In all of these studies, the increase in platelet count was reduced at and after the second dose during repeated dose of romiplostim compared with that after the initial dose; however, no such reduction was noted in the 1000 μg/kg group. Although these studies demonstrated that the production of antibodies against romiplostim reduced the pharmacological action of romiplostim, thrombocytopenia did not develop in any of the animals, suggesting no production of neutralizing antibodies against endogenous TPO.

3.(iii).A.(6).3) Tissue cross-reactivity (Attached document 4.2.3.7.7-1)

A preliminary study was conducted using human and cynomolgus monkey tissues as well as human megakaryocyte-derived cell line to establish the conditions for immunohistochemistry for evaluation of romiplostim. However, no tissue cross-reactivity study has been conducted because immunohistochemistry appeared not to be sensitive enough to detect the binding site of romiplostim.

3.(iii).A.(6).4) Formulation comparison studies

The frozen solution of romiplostim was used in the nonclinical and early clinical studies of romiplostim in the course of development. As the lyophilized product was developed later, formulation comparison studies were conducted in rats to compare the pharmacokinetics and pharmacological action (platelet-increasing effect) of these two formulations given as a single subcutaneous dose. No changes in general conditions including death were seen in these studies, indicating no difference in toxicological responses to the two formulations.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Excessive increase in platelet count

PMDA asked the applicant to explain the safety of romiplostim in humans and the necessity to alert physicians to the use of romiplostim in patients with a risk of thrombosis for the following reasons: deaths and worsened general conditions were observed in several rat toxicity studies; the dose of romiplostim that caused deaths (10 μg/kg/dose) and the exposure to romiplostim given as subcutaneous doses in the 4-week repeat-dose toxicity study were lower than that at the highest clinical dose (10 μg/kg/dose); and the results of the monkey studies suggested a possible risk of blood coagulation due to a high platelet count induced by romiplostim, as previously explained by the applicant.

The applicant explained as follows:

Since no toxicity studies in rat demonstrated clear toxicological change that might have reduced body weight gain, reduced body weight gain and decreased food consumption are likely to have resulted from an excessive and prolonged increase in platelet count. This can be explained by the following mechanism. (a) The first possible mechanism is the effect of increased circulating blood flow associated with an increased platelet count in blood. An increased platelet count and decreased erythrocytic parameters were reported in rats receiving PEG-rhuMGDF, as with romiplostim, which can be partially explained by increased circulating blood and plasma flow (Harada K et al. *J Pharmacy and Pharmacol.* 1999;51[7]:841-6). A similar mechanism is likely to operate with romiplostim; an acute increase in platelet count after the dose of romiplostim increased circulating blood flow to lead to worsened general conditions, maybe resulting in suppressed feeding behavior. (b) The other possible mechanism is the effect of increased blood viscosity associated with an increased platelet count. A high density of platelets increased blood viscosity, which may enhance potential blood coagulability or cause peripheral circulatory disturbance. The occurrence of vasomotor symptoms (e.g., headache, dizziness, tinnitus, paraesthesia) likely due to microvascular circulatory failure or infarction was reported in essential

thrombocythemia (Dan K et al. *Int J Hematol.* 2006;83[5]:443-9, Tefferi A et al. *Mayo Clin Proc.* 2001;76[1]:22-8). Likewise, romiplostim might have caused vasomotor symptom-like symptoms by enhancing the potential blood coagulability, maybe leading to suppressed feeding behavior.

Most of the deaths occurred on the day of or the day after blood sampling, suggesting that blood sampling induced the deaths. The platelet count in the 4-week repeat-dose toxicity study in rats was 2 to 2.5 times that in the vehicle group at 10 days after dosing in the subcutaneous 10 μg/kg group and 3.5 to 3.9 times in the subcutaneous 100 μg/kg group. All the deaths reported occurred 1 week or longer after first administration, i.e., approximately the time when the platelet count peaked, suggesting their relationship with increased platelet count. The rats that received romiplostim had a high platelet count. No thrombosis, infarction, or multiple microthrombi that might have explained the deaths was observed in the dead animals. However, eosinophilic substances, which appeared to be blood components that coagulated in a large blood vessel, were found in some of the animals, indicating potential enhancement of blood coagulability. Damage of the blood vessel caused by blood sampling or stress under restraint is likely to have stimulated blood coagulability to cause disseminated microvascular thrombosis and its associated vasomotor symptoms, leading to acute deaths.

In the 4-week repeat-dose toxicity study in rats, the blood concentration of romiplostim at the lowest dose that caused a death was below the lower limit of quantification, and therefore a relationship between death and exposure cannot be discussed. The risk can be avoided by monitoring platelet count in patients and maintaining it within an appropriate range. The draft package insert states periodic monitoring of platelet count and dose adjustment based on the platelet count in order to avoid the risk of severe thrombocythemia, which will be sufficient to promote awareness about the risk of thrombocythemia.

PMDA considers as follows:
Although the draft package insert includes the information that alerts physicians to the risk of thrombosis or thromboembolism and dose adjustment based on platelet count, appropriate caution should be provided, and the platelet count should be carefully monitored in patients, considering the pharmacological action of romiplostim, possible occurrence of thrombosis or vasomotor symptoms due to an acute increase in platelet count in humans, and the limited sample sizes in the clinical studies. It is also necessary to evaluate the safety of romiplostim continuously and carefully in post-marketing surveillance.

3.(iii).B.(2) Carcinogenicity

Since the applicant discussed that bone marrow fibrosis and hyperostosis in rats can be explained by increased transforming growth factor β (TGF-β) and platelet derived growth factor (PDGF) due to enhanced megakaryocytic hematopoiesis, PMDA asked the applicant to explain the possibility of any neoplastic change due to TGF-β or PDGF released from megakaryocytes associated with romiplostim injection.

The applicant responded as follows:
A study on excessive TPO expressing transgenic mice aged 18 months reported no neoplastic change despite higher TGF-β and PDGF-BB concentrations in blood than those in wild-type mice (Shimoda HK et al. *Am J Hematol.* 2007;82:802-6). As this study revealed changes in bone marrow similar to those observed in the repeat-dose toxicity studies in rats of romiplostim, this experimental model can be used to predict toxicities during repeated dose of romiplostim. Based on the results of the above study, increased TGF-β and PDGF associated with romiplostim injection is unlikely to affect tumor development. Additionally, mesangial proliferative nephritis, which occurred in excessive TPO expressing transgenic mice, was not reported in the toxicity studies of romiplostim, suggesting that an increase, if any, of TGF-β and PDGF level in bone marrow is not high enough to cause any systemic biological reaction. Furthermore, considering

that romiplostim caused no bone marrow fibrosis in monkeys or humans, although romiplostim-induced increases in TGF-β and PDGF cause bone marrow fibrosis or hyperostosis secondarily, the actual increase is almost negligible. Even if these changes potentially influence tumor development or metastasis, the increase at the clinical dose will be too low to induce tumor development or metastasis.

PMDA generally accepted the above explanations by the applicant. However, the potential for romiplostim to cause tumors cannot be ruled out, thus, PMDA considered that it is necessary to collect the latest knowledge regarding TGF-β and PDGF and long-term clinical data through post-marketing surveillances and to carefully evaluate them.

3.(iii).B.(3) Bone marrow fibrosis

PMDA asked the applicant to explain the thresholds of the dose and dosing period of romiplostim that induce bone marrow fibrosis and the intensity of reversible lesions in rats.

The applicant responded as follows:

Although it is difficult to determine the thresholds of the dose and dosing period of romiplostim because neutralizing-antibodies against romiplostim reduced the pharmacological action of romiplostim, dose-dependent bone marrow fibrosis in rats including hyperostosis resolved after the recovery period and it is deemed reversible. The type of fibers that increased was not identified and mature collagen fibers might have proliferated. However, these changes resolved completely, suggesting that they were different from bone marrow fibrosis in humans. No bone marrow fibrosis accompanied by collagen fiber proliferation was seen in monkeys. Therefore, there seems to be a safety margin between an increase in megakaryocyte or platelet count and the occurrence of bone marrow fibrosis.

PMDA considered as follows:

Although the draft package insert includes the information that alerts physicians to the risk of bone marrow fibrosis, it is necessary to continuously collect information regarding this event through post-marketing surveillances and to carefully evaluate it, considering the pharmacological action of romiplostim, the possibility for romiplostim to cause bone marrow fibrosis in humans, and the limited sample sizes in the clinical studies.

4. Clinical data

4.(i) Summary of biopharmaceutic studies

4.(i).A Summary of the submitted data

Concentrations of romiplostim and endogenous thrombopoietin (eTPO) in human serum were determined by ELISA.

4.(i).A.(1) Comparability between formulations

In the clinical studies for this application, P1 formulation produced by the manufacturing process for early clinical studies and P2 formulation produced by the manufacturing process for marketing were used. The pharmacokinetics and pharmacodynamics of the P1 and P2 formulations have been evaluated for comparability in 2 subgroups (Subsets A and B) in Foreign study 20030213.

4.(i).A.(1).1) Subset A in Study 20030213 (pharmacodynamic comparability)

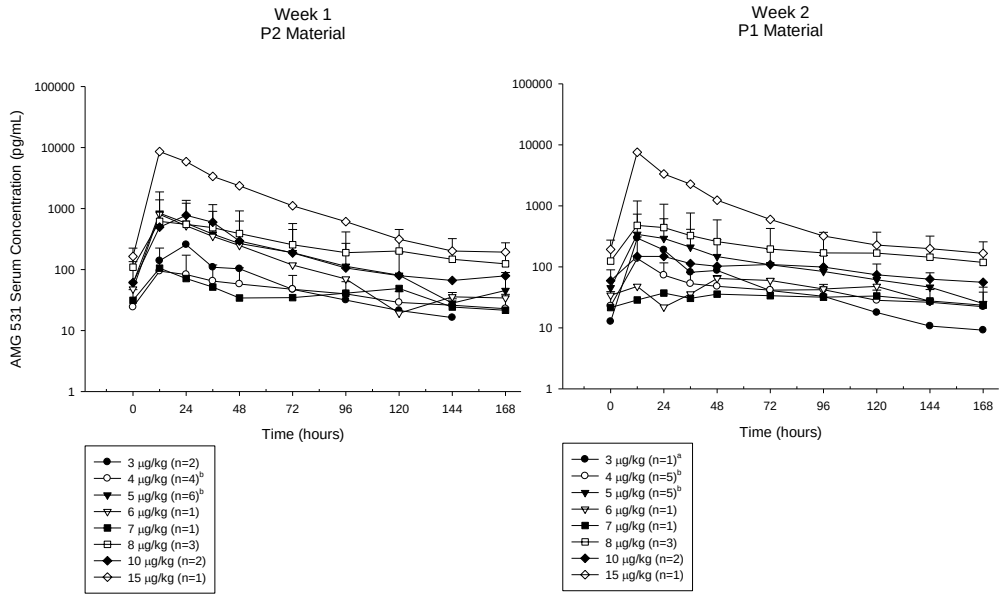
The dose of the P1 formulation of romiplostim was individually adjusted for each subject to maintain the platelet count >50,000 and ≤250,000/μL. The P1 formulation was subcutaneously administered once weekly for at least 20 weeks before switching to the P2 formulation at the same dose. After the first dose of the P2 formulation, the dose was then individually adjusted for each subject to continue the study treatment. Of them, 22 ITP patients who continued the study

treatment for at least 3 months were included in the subset. The doses before and after switching were 1.0 to 17.0 μg/kg and 0.2 to 17.0 μg/kg, respectively. The platelet counts measured once weekly during a period of 30 days in total before (P1 formulation) and after (P2 formulation) switching were 111,130 ± 76,190 (mean ± standard deviation [SD]) and 113,910 ± 82,280/μL, respectively. The doses were 7.58 ± 5.82 μg/kg and 7.43 ± 5.89 μg/kg, respectively. The percentages of the subjects who were reported to receive the salvage therapy (corticosteroid, human immunoglobulin G for intravenous injection [IVIgG], etc.) and of those who changed the dose at least once were almost comparable between the 2 groups.

4.(i).A.(1).2) Subset B in Study 20030213 (pharmacokinetic comparability)

To ITP patients who were enrolled in Study 20030213 and had subcutaneously received the P2 formulation at the doses ≥3 μg/kg at least 3 times consecutively, the P2 formulation of romiplostim was subcutaneously administered at Week 1 of dosing (Day 1) followed by subcutaneous administration of the P1 formulation at the same dose as that of the P2 formulation at Week 2 of dosing (Day 8). Blood samples were collected from each subject at 19 time points on 15 consecutive days (n = 19). The dose of romiplostim ranged from 3 to 15 μg/kg.

The serum romiplostim concentrations over time following administration of the P1 and P2 formulations were as shown in Figure 2.



a: Not measured due to problematic handling of 6 clinical specimens at Week 2 of dosing.
b: The dose was changed between Weeks 1 and 2.

Figure 2. Serum romiplostim concentrations over time following administration of the P1 and P2 formulations (mean + SD) (partially modified from the submitted data)

In the pharmacokinetics of romiplostim, as with eTPO, clearance mediated by the TPO receptor on the surface of platelets and megakaryocytic cells are suggested to be involved (Li J et al. *Br J Haematol.* 1999;106:345-56). The pharmacokinetic comparability was evaluated using the mixed-effects model including the drug products (P1 formulation, P2 formulation) as fixed effects, subjects as random effects, and the baseline platelet count as a covariate to take the effect of the platelet count on serum romiplostim concentration into consideration. The mixed-effects model used in this analysis was as described below.

$\log (AUC) = \text{subjects} + b \times \log (\text{baseline platelet count}) + \text{drug product} + \varepsilon$
$\log (C_{max}) = \text{subjects} + b \times \log (\text{baseline platelet count}) + \text{drug product} + \varepsilon$

As a result of the analysis, the point estimate of the ratio of mean AUC of the P2 formulation to that of the P1 formulation was 1.17 with the 90% confidence interval (CI) of the ratio being 0.98 to 1.41. The point estimate of the ratio of mean C_{max} was 1.33 with the 90% CI being 1.01 to 1.74.

4.(i).B. Outline of the review by PMDA

In the Japanese phase III study and Japanese long-term treatment study, the P2 formulation, which was to be marketed, was used, while the P1 formulation was used in the foreign phase III studies.

PMDA considers the differences between the P1 and P2 formulations as follows:
The pharmacokinetics of romiplostim is affected by the platelet count in subjects who have received romiplostim and it is difficult to demonstrate bioequivalence between the formulations by comparison of the bioavailability of romiplostim. However, the pharmacokinetics of the P1 and P2 formulations were suggested to be equivalent by the pharmacodynamic comparison based on the platelet count and pharmacokinetic comparison using model analysis. PMDA has thus concluded that the difference in the drug product formulations does not become a problem in referring to the data from clinical studies with the P1 formulation.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

Of clinical studies submitted in this application, those in which serum romiplostim concentrations were measured included 2 studies in healthy adult subjects as well as Study 20000137B (Foreign study) for dose-finding in ITP patients, 3 phase III studies (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212), 2 long-term extension studies (Japanese study 20[redacted]0113, Foreign study 20030213), 2 phase IIIb studies (Foreign studies 20060131 and 20040209), and Study 20060195 (Foreign study) in pediatric chronic ITP patients. The major study data that allow pharmacokinetic and pharmacodynamic evaluation are shown below.

4.(ii).A.(1) Investigations in healthy adult subjects

4.(ii).A.(1).1) Japanese phase I study (Attached document 5.3.4.1-2, Study 20040134)

Following single subcutaneous doses of romiplostim 0.3, 1, or 2 μg/kg to 24 healthy adult male subjects (8 subjects per group), the serum romiplostim concentrations were measured at the dose of 2 μg/kg, but the pharmacokinetic parameters could not be calculated because only a part of the results from 2 subjects (6 time points in total) were above the lower limit of quantification (18 pg/mL).

The platelet counts over time following a single subcutaneous administration of romiplostim and placebo were as shown in Figure 3.

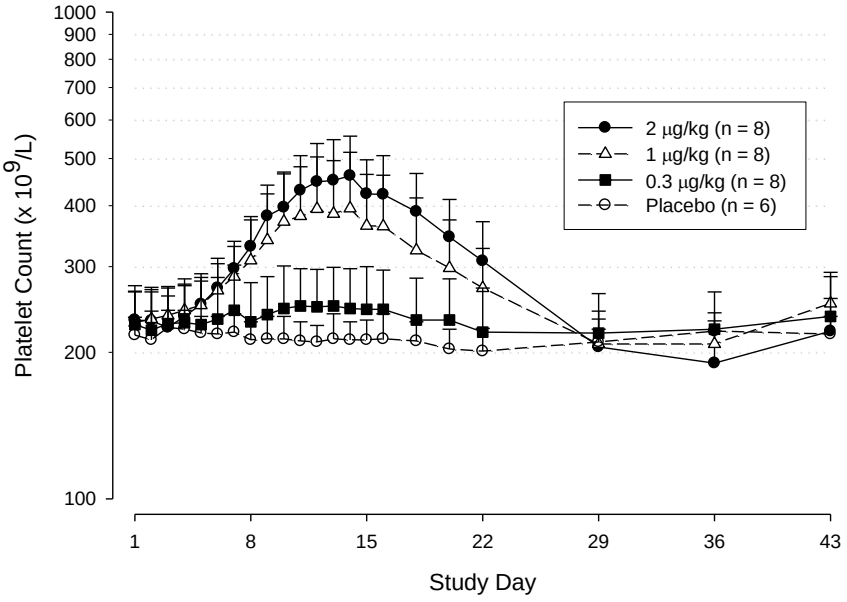


Figure 3. Platelet counts over time in healthy adult subjects following a single subcutaneous administration of romiplostim (Study 20040134, mean + SD)
(partially modified from the submitted data)

Since the platelet count increased to ≥ twice the baseline at 2 consecutive time points in ≥2 subjects (3 subjects) following a single subcutaneous dose of romiplostim 2 μg/kg, the dose was not increased to 3 μg/kg.

4.(ii).A.(1).2) Foreign phase I study (Attached document 5.3.4.1-1, Study 20000109)
A single intravenous dose of romiplostim 0.3, 1, or 10 μg/kg was administered to 12 healthy adult male subjects (4 subjects per group). The serum romiplostim concentration immediately after dosing (C_0) was 2810 ± 1170, 12,900 ± 1760, and 211,000 ± 32,000 pg/mL at the respective doses above, $AUC_{0\text{-}t}$ was 669 ± 732, 26,500 ± 19,000, and 1,520,000 ± 260,000 pg·hr/mL at the respective doses above, and $t_{1/2}$ was 1.50 ± 2.83, 2.41 ± 1.56, and 13.8 ± 3.89 hours at the respective doses above.

Following a single subcutaneous dose of romiplostim 0.1, 0.3, or 1 μg/kg to 12 healthy adult male subjects (4 subjects per group), the serum romiplostim concentrations were below the lower limit of quantification (18 pg/mL) at all blood sampling time points in all subjects.

A single subcutaneous dose of romiplostim 2 μg/kg was administered to 8 healthy adult male subjects. As the serum romiplostim concentration was quantifiable at some of the blood sampling time points in 5 subjects, the C_{max} was found between 24 and 36 hours post-dose, but the $t_{1/2}$ and F could not be calculated.

In this study, the mean baseline platelet count was 201,000 to 259,000/μL. Following a single intravenous or subcutaneous dose to healthy adult subjects, the platelet count increased dose-dependently. The platelet count peaked at 11 to 15 days post-dose for intravenous and subcutaneous administrations. The platelet count then returned to the baseline level 27 days post-dose. For both intravenous and subcutaneous administrations, the dose of 1 μg/kg was determined to be the minimum effective dose (defined as a dose at which the platelet count increased to ≥1.5 times the baseline at 2 consecutive points among scheduled time points in 2 subjects), and in

clinical studies in ITP patients conducted after this study, a subcutaneous dose of 1 μg/kg was chosen as the initial dose.

4.(ii).A.(2) Investigation in patients

4.(ii).A.(2).1) Japanese clinical study (Attached document 5.3.5.2-2, Study 20[redacted]0113)

The serum romiplostim concentrations were measured in 4 adult chronic ITP patients, who were enrolled in the Japanese long-term extension study (Study 20[redacted]0113) and showed a platelet count ≥50,000/μL on the day of dosing. The serum concentrations over time after administration of romiplostim at the doses of 5 to 7 μg/kg (individual values) were as shown in Figure 4.

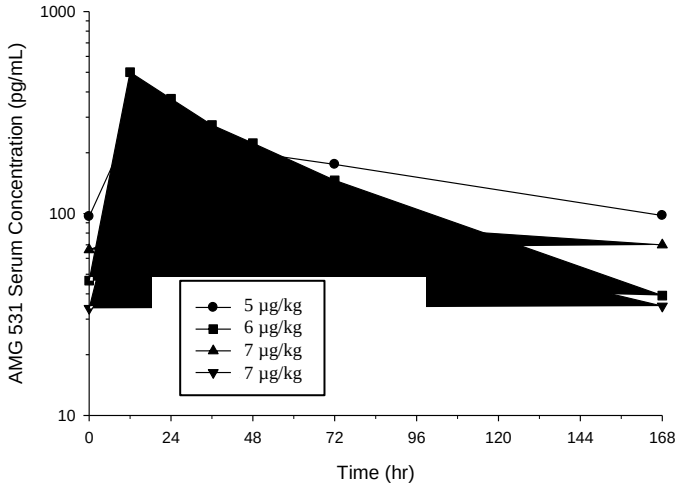


Figure 4. Individual serum romiplostim concentrations over time in adult chronic ITP patients who received multiple subcutaneous doses once weekly (Study 20[redacted]0113)
(partially modified from the submitted data)

The $AUC_{0\text{-}168}$ and C_{max} were neither dose-dependent nor correlated to the platelet count. The $t_{1/2}$ was 47.6 to 116 hours in 3 of 4 patients (it could not be calculated in 1 patient).

4.(ii).A.(2).2) Foreign clinical study

(a) Study 20030105 (Attached document 5.3.5.1-1)

Romiplostim was subcutaneously administered once weekly to 8 splenectomized adult ITP patients, and 15 serum samples were collected. Of these, 14 samples were assayed for the serum romiplostim concentration on Day 8 ± 1 (with the day of dosing as Day 1) (the serum romiplostim trough concentration), which were 23.7 to 46.9 pg/mL (5 samples from 5 patients) at the dose of 9 μg/kg, 20.8 and 88.1 pg/mL (2 samples from 2 patients) at the dose of 11 μg/kg, 70.9 pg/mL (1 sample from 1 patient) at the dose of 14 μg/kg, and 44.5 to 92.7 pg/mL (6 samples from 1 patient) at the dose of 15 μg/kg. The concentration in 1 sample at the dose of romiplostim 1 μg/kg was below the lower limit of quantitation (18.614 pg/mL).

(b) Study 20030212 (Attached document 5.3.5.1-2)

Romiplostim was subcutaneously administered once weekly to 4 non-splenectomized adult ITP patients, and 4 serum samples were collected. Of these, 3 samples were assayed for the serum romiplostim trough concentration, which were 20.9 and 162 pg/mL (2 samples from 2 patients) at the dose of 9 μg/kg and 82.7 pg/mL (1 sample from 1 patient) at the dose of 10 μg/kg. The concentration in 1 sample at the dose of romiplostim 1 μg/kg was below the lower limit of quantitation (18.614 pg/mL).

(c) Study 20030213 (Attached document 5.3.5.2-1)

Romiplostim was subcutaneously administered once weekly to 31 ITP patients, and 36 serum samples were collected. Of these, 14 samples were assayed for the serum romiplostim concentration. The serum romiplostim trough concentration was 27.4 to 168 pg/mL (4 samples from 4 patients) at the dose of 9 μg/kg, 21.7 to 109 pg/mL (5 samples from 5 patients) at the dose of 10 μg/kg, 1190 pg/mL (1 sample from 1 patient) at the dose of 13 μg/kg, 29.1 and 44.5 pg/mL (2 samples from 2 patients) at the dose of 15 μg/kg, and 104 pg/mL (1 sample from 1 patient) at the dose of 18 μg/kg. The concentrations in 22 samples from 21 patients at the doses of romiplostim 1 to 11 μg/kg were below the lower limit of quantitation (18.614 pg/mL). The serum romiplostim concentration determined at the non-trough time point was 51.6 pg/mL (Day 3) at the dose of 10 μg/kg.

(d) Study 20040209 (Attached document 5.3.5.4-1)

Romiplostim was subcutaneously administered once weekly to 34 adult ITP patients, and 59 serum samples were collected. Of these, 23 samples were assayed for the serum romiplostim concentration. The serum romiplostim trough concentration was 29.0 pg/mL (1 sample from 1 patient) at the dose of 4 μg/kg, 29.5 and 86.9 pg/mL (2 samples from 2 patients) at the dose of 8 μg/kg, 19.6 to 126 pg/mL (9 samples from 8 patients) at the dose of 9 μg/kg, and 21.4 to 287 pg/mL (7 samples from 5 patients) at the dose of 10 μg/kg. The concentrations in 36 samples from 18 patients at the doses of romiplostim 1 to 10 μg/mL were below the lower limit of quantitation (18.614 pg/mL). The serum romiplostim concentrations determined at the non-trough time point were 23.1 pg/mL (Day 1) at the dose of 11 μg/kg, 35.2 pg/mL (Day 42) at the dose of 10 μg/kg, 68.2 pg/mL (Day 5) at the dose of 10 μg/kg, and 91.9 pg/mL (Day 3) at the dose of 11 μg/kg.

(e) Study 20060131 (Attached document 5.3.5.4-3)

Romiplostim was subcutaneously administered once weekly to 20 non-splenectomized adult ITP patients, and 53 serum samples were collected. Of these, 39 samples were assayed for the serum romiplostim concentration. The serum romiplostim trough concentration was 38.4 pg/mL (1 sample from 1 patient) at the dose of 2 μg/kg, 16.8 to 44.6 pg/mL (12 samples from 4 patients) at the dose of 3 μg/kg, 18.1 to 33.2 pg/mL (8 samples from 3 patients) at the dose of 4 μg/kg, 23.4 to 33.4 pg/mL (6 samples from 1 patient) at the dose of 5 μg/kg, 22.9 pg/mL (1 sample from 1 patient) at the dose of 6 μg/kg, 45.0 pg/mL (1 sample from 1 patient) at the dose of 7 μg/kg, 60.9 pg/mL (1 sample from 1 patient) at the dose of 9 μg/kg, and 37.3 to 84.3 pg/mL (5 samples from 3 patients) at the dose of 10 μg/kg. The concentrations in 14 samples from 7 patients at the doses of romiplostim 1 to 4 μg/mL were below the lower limit of quantitation (15 pg/mL). The serum romiplostim concentrations determined at the non-trough time point were 28.7 pg/mL (Day 1) at the dose of 3 μg/kg, 37.4 pg/mL (Day 1) at the dose of 4 μg/kg, 46.2 pg/mL (Day 5) at the dose of 3 μg/kg, and 114 pg/mL (Day 4) at the dose of 10 μg/kg.

(f) Study 20060195 (Attached document 5.3.5.4-4)

Romiplostim was subcutaneously administered once weekly to 14 pediatric chronic ITP patients, and these patients entered the pharmacokinetic evaluation period. The serum concentrations were measured before dosing on the day of dosing (Day 1) and on Day 3 between Weeks 13 and 16. Children aged ≥12 months and <3 years, ≥3 years and <12 years, and ≥12 years and <18 years received romiplostim at the doses of 1 to 7, 3 to 10, and 1 to 10 μg/kg, respectively. Of 67 samples collected before each dosing at Week 12 or later, 32 samples were assayed for the serum romiplostim concentration with the range from 16.0 to 51.1 pg/mL. Of 60 samples collected on each Day 3 at Week 12 or later, 44 samples were assayed for the serum romiplostim concentration with the range from 17.7 to 274 pg/mL. The serum romiplostim concentrations at the dose of romiplostim <3 μg/kg were below the lower limit of quantification (15 pg/mL) at all time points.

4.(ii).A.(3) Pharmacodynamic study

4.(ii).A.(3).1) Study 20000109

The serum eTPO concentrations over time following single intravenous or subcutaneous dose of romiplostim measured in the foreign phase I study (Study 20000109) are as shown in Figure 5.

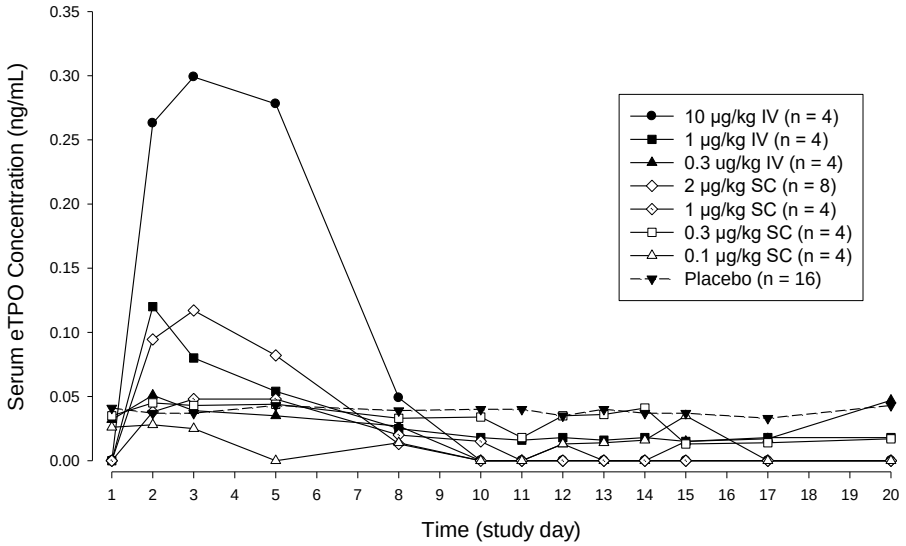


Figure 5. Serum eTPO concentrations over time in healthy adult subjects following single intravenous or subcutaneous dose of romiplostim (Study 20000109, median) (partially modified from the submitted data)

4.(ii).A.(3).2) Study 20030105

The median serum eTPO concentration at the baseline (normal range, 32-246 pg/mL) was 124 pg/mL in the placebo group and 113 pg/mL in the romiplostim group, and no difference was found between them. At Week 25, the concentration in the placebo group remained almost unchanged with the median of 112.8 pg/mL, while in the romiplostim group, it markedly decreased to the median of 69.9 pg/mL.

4.(ii).A.(3).3) Study 20030212

The median serum eTPO concentration at the baseline (normal range, 32-246 pg/mL) was 81.4 pg/mL in the placebo group and 93.8 pg/mL in the romiplostim group, and no difference was found between them. At Week 25, the concentration in the placebo group slightly decreased to the median of 64.3 pg/mL, while in the romiplostim group, it markedly decreased to the median of 48.8 pg/mL.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Pharmacokinetic characteristics of romiplostim and pharmacokinetic-pharmacodynamic (PK/PD) relationship

Following intravenous doses of romiplostim to foreign healthy adult subjects, the C_0 and AUC_{0-t} increased more than dose-proportionally.

The applicant explained the reason for such an increase as follows:
In the pharmacokinetics of romiplostim, as with eTPO, clearance mediated by the TPO receptor on the surface of platelets and cells of the thrombopoietic lineage such as megakaryocytes is suggested to be involved (Li J et al. *Br J Haematol*. 1999;106:345-56). Therefore, the

pharmacokinetics of romiplostim can be non-linear due to saturation of the binding of romiplostim to the TPO receptor.

Also, the applicant explained the difference in pharmacokinetics of romiplostim between healthy adult subjects and ITP patients as follows:
In Study 20000137B in which multiple subcutaneous doses of romiplostim 1 μg/kg were administered to foreign adult ITP patients, the serum romiplostim concentrations exceeded the lower limit of quantification at ≥1 time point in 5 of 8 patients. In contrast, in a foreign clinical study in which a single subcutaneous dose of romiplostim 1 μg/kg was administered to the foreign healthy adult subjects, the serum romiplostim concentrations were below the lower limit of quantification at all blood sampling time points. Because platelets seemed to play an important role in the elimination of romiplostim, the difference in serum romiplostim concentration between the healthy adult subjects and adult ITP patients was considered attributable to the difference in platelet count. In these foreign clinical studies, the baseline platelet count in chronic ITP patients (<30,000/μL) was lower than that in healthy adult subjects (201,000-259,000/μL). Based on the above, the serum romiplostim concentration over time can remain higher in adult ITP patients than in healthy adult subjects.

Although there were large differences in pharmacokinetic parameters such as C_{max} and AUC following a single dose between the intravenous and subcutaneous routes, the increases in platelet count were comparable between the intravenous and subcutaneous routes at the same dose level. PMDA asked the applicant to explain the reasons for such a thrombopoietic effect.

The applicant explained as follows:
Different administration routes are unlikely to have different effects on the mechanism of the clearance mediated by the TPO receptor on the surface of platelets and cells of the thrombopoietic lineage such as megakaryocytes, and the absorption process after a subcutaneous dose of romiplostim might influence the serum romiplostim concentration, causing the difference between the routes. In Study 20000109, the serum romiplostim concentrations following subcutaneous doses at 0.1 to 1 μg/kg were all below the lower limit of quantification, but the serum eTPO concentration increased dose-dependently at Week 1 as observed following intravenous doses of romiplostim 0.3 to 10 μg/kg (Figure 5). Because romiplostim and eTPO competitively bind to the TPO receptor, romiplostim could bind to the TPO receptor by replacing eTPO with increasing dose with either administration route, resulting in saturation of receptor-mediated clearance. The platelet counts over time following intravenous or subcutaneous administration of romiplostim were both dose-dependent, while pharmacokinetic parameters such as C_{max} and AUC following single administration differed between the two administration routes. The above findings were also observed not only in rats and monkeys but also in other drugs such as recombinant human erythropoietin and granulocyte colony-stimulating factor. The reasons are considered to be as follows: as the serum romiplostim concentration is high immediately after the intravenous administration, leading to saturation of the TPO receptor with romiplostim, increase in the serum romiplostim concentration cannot be reflected in the PD response; or as the serum romiplostim concentration is low immediately after the subcutaneous administration, allowing romiplostim to activate the TPO receptor effectively without the saturation of their binding, thrombopoiesis can be enhanced.

The PK/PD relationship between the serum romiplostim concentration and platelet count was analyzed using the E_{max} model, in which the cumulative drug effects following the intravenous and subcutaneous doses were expressed as the function between the serum romiplostim concentration beyond a threshold (SC_{50}) and time. The exposure correlated to the PD response is thus not based on the C_{max} or AUC but based on the period in which the serum romiplostim concentration was above the threshold. The comparable platelet counts over time in rats which received intravenous or subcutaneous doses of romiplostim 100 μg/kg can be explained by the

fact that the serum romiplostim concentrations following intravenous or subcutaneous doses remained above the SC_{50} (15.5 ng/mL), estimated from the PK/PD model, for approximately the same period of 60 hours. Similarly, the comparable platelet counts over time in rhesus monkeys which received intravenous or subcutaneous doses of romiplostim 2000 μg/kg can be explained by the fact that the serum romiplostim concentrations remained above the SC_{50} (944 ng/mL), estimated from the PK/PD model, for approximately the same period of 50 hours. In Study 20000109, the minimum effective dose of romiplostim subcutaneously administered was confirmed to be 1 μg/kg, and at this dose, the serum romiplostim concentration was below the lower limit of quantification (18 pg/mL) at any time point. It was thus suggested that the serum romiplostim concentration necessary for the increase in platelet count is considerably low.

The above data suggest that the exposure correlated to the platelet-increasing effect is based on the period in which the serum romiplostim concentration is above a threshold. With the same exposure period, both intravenous and subcutaneous doses provided the comparable platelet counts over time although the pharmacokinetic parameters such as C_{max} and AUC were different between these administration routes.

PMDA considers as follows:
As the exposure following intravenous administration was 40 times that following subcutaneous administration, it is considered difficult to explain the decrease of F following subcutaneous administration only with the influence of the absorption process. Although the applicant explained that the mechanism based on the receptor saturation might be related to the different responses between the two administration routes, PMDA cannot agree to the applicant's explanation in consideration that the platelet counts over time following intravenous administration of romiplostim were also found to be dose-dependent. Accordingly, the applicant's explanation is not sufficient enough to clarify why the increases in platelet count following the intravenous and subcutaneous administrations were comparable at the same dose level despite their resultant exposures being different. Since the platelet count increased with increasing dose in subcutaneous administration of romiplostim, it can be managed to some extent by increasing the dose with expectation of the effect or deceasing it in response to the increased platelet count. The correlation between the serum romiplostim concentration and platelet count, however, is hardly demonstrated by the study data. It is difficult to predict the serum romiplostim concentration from the dose or the platelet count from the serum romiplostim concentration uniformly in each subject based only on a model. Thus, it is essential to monitor the platelet count during the romiplostim treatment. The frequency of monitoring and the appropriateness of the dose adjustment procedure during the romiplostim treatment will be reviewed in the clinical data section.

4.(ii).B.(2) Difference in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects

Romiplostim is planned to be indicated for a rare disease and the number of patients included in Japanese clinical studies was limited. In order for PMDA to consider the feasibility of assessing the efficacy and safety of romiplostim taking into account the foreign clinical study data additionally, PMDA asked the applicant to investigate the differences in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects so that whether or not such an evaluation is acceptable would be made clear.

The applicant explained as follows:
Although the number of subjects was limited (4 Japanese subjects, 11 foreign subjects), the Japanese and foreign long-term extension studies (Japanese study 20[redacted]0113, Subject B of the Foreign study 20030213) in adult ITP patients showed that the serum romiplostim concentrations over time and pharmacokinetic parameters in the Japanese subjects fell within ranges of the results in foreign subjects at the same dose range. In the pharmacokinetics of romiplostim, as with eTPO, the clearance mediated by the TPO receptor on the surface of platelets and cells of the

thrombopoietic lineage such as megakaryocytes seemed to be involved. The relationship between the baseline (before dosing) platelet count and apparent clearance (CL/F) as well as that between the serum romiplostim trough concentration and corresponding platelet count following multiple subcutaneous doses of romiplostim were investigated in Japanese and foreign subjects in whom the serum romiplostim trough concentrations and corresponding platelet counts had been obtained at the same dose range (5-10 μg/kg). As a result, the comparison between Japanese and foreign subjects with the similar baseline platelet counts was difficult for the relationship between the baseline platelet count and CL/F at each dose level because the number of the appropriate subjects was limited. The investigation failed to provide the results suggesting the positive correlation in which the CL/F increased with the increasing baseline platelet count. On the other hand, for the relationship between the baseline platelet count and serum romiplostim trough concentration, the higher platelet count tended to be related to the lower serum romiplostim trough concentration irrespective of the dose level (5-10 μg/kg), which were found in both Japanese and foreign subjects. Accordingly, no major differences were noted in pharmacokinetics between Japanese and foreign adult ITP patients.

In the foreign phase II (Study 20000137B) study and Japanese phase II study (Study 20050162) in adult chronic ITP patients, their main inclusion criteria were the same, and romiplostim was subcutaneously administered at the common dose levels (1, 3, 6 μg/kg) on Days 1 and 8. As for pharmacodynamics, there were no marked differences in platelet count before dosing on Day 1 (Predose), Day 8, or Day 15 or in baseline-normalized platelet count on these days between Japanese and foreign patients, and the scatter plots of individual platelet count were similar between Japanese and foreign patients. In addition, data from the Japanese and foreign phase III studies in ITP patients in which the dose of romiplostim was adjusted to the target platelet count of 50,000 to 200,000/μL (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212) were evaluated. Although the platelet counts and dose levels were different between Japanese and foreign studies until Week 9 due to the different initial doses (3 μg/kg in the Japanese study, 1 μg/kg in the foreign studies), the platelet counts and dose levels at Week 10 and afterward were comparable between these studies. Based on the above, the pharmacodynamic profiles of romiplostim subcutaneously administered to adult ITP patients were considered not to be significantly different between Japanese and foreign patients.

PMDA considers as follows:
The pharmacokinetics of romiplostim can be characterized by non-dose-dependent serum concentrations, large inter-individual variability even at the same dose, and CL/F affected by the platelet count. In clinical studies in Japanese and foreign patients, the relationship between the platelet count and serum romiplostim concentration was investigated in the limited number of patients. In particular, the applicant explained that the higher platelet count tended to be associated with the lower serum romiplostim trough concentration in both Japanese and foreign patients. However, the tendency was hardly shown in 4 patients in Japanese study 20[redacted]0113. Therefore, the pharmacokinetics of romiplostim cannot be considered comparable between Japanese and foreign patients. On the other hand, the serum romiplostim concentrations over time in ITP patients who received a single subcutaneous dose was comparable between Japanese study 20[redacted]0113 and Foreign study 20030213. Therefore, the serum romiplostim concentrations in the Japanese clinical study fell within the range of the concentrations in the foreign clinical study (Figures 2 and 4). Although it is difficult to determine that the platelet counts over time are comparable between Japanese and foreign subjects due to the limited numbers of the subjects included in the investigation, the applicant's explanation cannot be ruled out that the pharmacodynamic profiles of romiplostim administered subcutaneously are comparable between Japanese and foreign adult ITP patients. The above discussion does not suggest that the difference between Japanese and foreign subjects in the Japanese and foreign clinical studies prevents foreign clinical study data from being referenced for evaluation of the efficacy and safety of romiplostim in Japanese subjects.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A. Summary of the submitted data

As the evaluation data, the results from a total of 15 studies including the following studies were submitted: 1 each of the phase I study, phase II study, phase III study, and long-term extension study conducted in Japan; 1 phase I study, 3 phase I/II studies, 1 phase II study, 2 phase III studies, 2 phase IIIb studies, 1 long-term extension study, and 1 other supplemental study conducted in foreign countries [for the pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies" and "4.(ii) Summary of clinical pharmacology studies"]. The major study data are shown below.

4.(iii).A.(1) Phase I/II studies

4.(iii).A.(1).1) Foreign study 20000137A (Attached document 5.3.4.2-1, Studied period July 2002 to October 2003)

An open-label study in adult ITP patients was conducted at 5 centers in the U.S. to evaluate the safety and tolerability of romiplostim.

Romiplostim 0.2, 0.5, 1.0, 3.0, 6.0, or 10.0 μg/kg was to be subcutaneously administered to 4 patients in each group up to twice: after the first dose (Day 1), the second dose was to be administered on Day 15 to the patients in whom the platelet count on that day was ≤50,000/μL, or to be administered on Day 22 to the patients in whom it was >50,000/μL on Day 15 but ≤50,000/μL on Day 22; to the patients in whom the platelet count was >50,000/μL on both Day 15 and Day 22 or the maximum platelet count was >450,000/μL, the second dose was not to be administered. The study treatment was started first in the lowest dose group, and proceeding to the next higher dose level of treatment was determined based on the safety and efficacy data of the previous dose group.

The main inclusion criteria were as follows: patients who had completed at least one type of ITP therapy; and of 3 platelet counts measured during the screening period and before dosing, 2 counts (including the count on Day -2) were <30,000/μL if the patients did not receive the ITP therapy during the screening period; or the 2 counts were <50,000/μL if the patients regularly received corticosteroids at a fixed dose.

A total of 24 subjects were enrolled, and 4 subjects each were assigned to the romiplostim 0.2, 0.5, 1.0, 3.0, 6.0, or 10.0 μg/kg groups. All of them received romiplostim. A total of 4 subjects did not receive the second dose of romiplostim due to the treatment of an adverse event (1 subject in the 0.2 μg/kg group); meeting of the discontinuation criteria for the second dose rule (1 subject in the 6.0 μg/kg group, 2 subjects in the 10.0 μg/kg group). Of these, 1 subject in the 10.0 μg/kg group was lost to follow-up and discontinued the study, and 23 patients completed the study.

For the safety, no clear differences were found in incidence of adverse events among the doses, and data on the adverse events were pooled into two groups such as low doses (romiplostim 0.2, 0.5, 1.0 μg/kg) and high doses (romiplostim 3.0, 6.0, 10.0 μg/kg). The primary endpoints for the safety were set as the incidences and severities of all adverse events as well as the antibody production. The incidence of all adverse events was 100% at both low and high doses (12 of 12 subjects), and the adverse events with an incidence of ≥10% of all the subjects are listed in Table 1. For the severity, most of the adverse events were mild or moderate, and the incidence of severe adverse events was 8% (1 of 12 subjects) at the low doses and 25% (3 of 12 subjects) at the high doses.

Table 1. Adverse events reported by ≥10% of all the subjects (partially modified from the submitted data)

	Romiplostim (μg/kg)		Total (n = 24)
	Low doses: 0.2-1.0 (n = 12)	High doses: 3.0-10.0 (n = 12)	
Number of subjects with any adverse event	12 (100)	12 (100)	24 (100)
Contusion	3 (25)	9 (75)	12 (50)
Headache	6 (50)	5 (42)	11 (46)
Fatigue	5 (42)	3 (25)	8 (33)
Petechiae	3 (25)	5 (42)	8 (33)
Upper respiratory tract infection NOS	4 (33)	2 (17)	6 (25)
Arthralgia	3 (25)	1 (8)	4 (17)
Dizziness	1 (8)	3 (25)	4 (17)
Ecchymosis	3 (25)	1 (8)	4 (17)
Rash NOS	3 (25)	1 (8)	4 (17)
Ejaculation disorder NOS [a]	1 (25)	0 (0)	1 (14)
Epistaxis	1 (8)	2 (17)	3 (13)
Gingival bleeding	1 (8)	2 (17)	3 (13)
Nausea	3 (25)	0 (0)	3 (13)
Oedema peripheral	1 (8)	2 (17)	3 (13)
Oral mucosal blistering	1 (8)	2 (17)	3 (13)
Purpura NOS	2 (17)	1 (8)	3 (13)

a) calculation of the incidence in male subjects n (%)

No deaths were reported, and the incidence of the other serious adverse events was 50.0% (2 of 4 subjects) in the 0.2 μg/kg group and 25.0% (1 of 4 subjects) in the 10.0 μg/kg group. In all of the subjects who received romiplostim, no neutralizing antibodies against romiplostim or TPO were detected.

4.(iii).A.(1).2) Foreign study 20010218 (Attached document 5.3.4.2-2, Studied period, December 2002 to July 2004)

An open-label study in adult ITP patients was conducted at a total of 6 centers in the UK, France, or the Netherlands to evaluate the safety and tolerability of romiplostim.

Romiplostim 30, 100, 300, or 500 μg was to be subcutaneously administered up to twice. The second dose was to be administered on Day 15 to the patients in whom the maximum platelet count was ≤450,000/μL, the platelet count on that day was ≤50,000/μL, and the platelet count did not increase (the platelet count did not increase by >15,000/μL in the last 2 consecutive counts including on Day 15) or the second dose was to be postponed until Day 22 for the patients in whom the maximum platelet count was >50,000/μL and ≤450,000/μL, and the platelet count on Day 15 was >50,000/μL. The second dose was to be canceled when serious adverse events for which a causal relationship to the treatment could not be ruled out were reported or the platelet count on Day 22 was >50,000/μL. The study treatment was started first in the lowest dose group, and proceeding to the next higher dose level of treatment was determined based on the safety and efficacy data at the previous dose.

The main inclusion criteria were as follows: patients who had completed at least one type of ITP therapy; and of 3 platelet counts measured during the screening period and before dosing, 2 counts (including the count on Day -2) were <30,000/μL if the patients did not receive the ITP therapy during the screening period; or the 2 counts were <50,000/μL if the patients received corticosteroids at a fixed dose.

A total of 16 subjects were enrolled and assigned to the romiplostim 30 μg group (4 subjects),

100 μg group (4 subjects), 300 μg group (7 subjects), and 500 μg group (1 subject). All of them received romiplostim. In the first subject in the 500 μg group, the platelet count was increased to 1,062,000/μL on Day 17. In response to that, assignment of new subjects to the 500 μg group was suspended, and the remaining 3 subjects initially planned to be assigned to the 500 μg group were re-assigned to the 300 μg group. One subject each in the 300 and 500 μg groups did not receive the second dose due to the increase of the platelet count that met the discontinuation criteria for the second dose rule.

The primary endpoints for the safety were set as the incidences and severities of all adverse events as well as the antibody production. The incidence of all adverse events was 100% at any dose, and the adverse events reported by ≥2 subjects from all groups are listed in Table 2. The incidence of severe adverse events was 29% (2 of 7 subjects) in the 300 μg group and 100% (1 of 1 subject) in the 500 μg group.

Table 2. Adverse events reported by ≥2 subjects (partially modified from the submitted data)

MedDRA ver 8.0 PT	Romiplostim (μg)				Total (n = 16)
	30 (n = 4)	100 (n = 4)	300 (n = 7)	500 (n = 1)	
Number of subjects with any adverse event	4 (100)	4 (100)	7 (100)	1 (100)	16 (100)
Headache	0 (0)	3 (75)	4 (57)	1 (100)	8 (50)
Arthralgia	0 (0)	2 (50)	3 (43)	0 (0)	5 (31)
Contusion	0 (0)	2 (50)	2 (29)	0 (0)	4 (25)
Epistaxis	1 (25)	1 (25)	2 (29)	0 (0)	4 (25)
Fatigue	0 (0)	1 (25)	3 (43)	0 (0)	4 (25)
Petechiae	0 (0)	2 (50)	1 (14)	1 (100)	4 (25)
Ecchymosis	1 (25)	1 (25)	1 (14)	0 (0)	3 (19)
Injection site haemorrhage	1 (25)	1 (25)	1 (14)	0 (0)	3 (19)
Nasopharyngitis	0 (0)	1 (25)	2 (29)	0 (0)	3 (19)
Oedema peripheral	0 (0)	0 (0)	3 (43)	0 (0)	3 (19)
Back pain	1 (25)	0 (0)	0 (0)	1 (100)	2 (13)
Diarrhoea	1 (25)	0 (0)	1 (14)	0 (0)	2 (13)
Haematoma	0 (0)	0 (0)	1 (14)	1 (100)	2 (13)
Mouth haemorrhage	0 (0)	0 (0)	2 (29)	0 (0)	2 (13)
Oral mucosal petechiae	0 (0)	1 (25)	1 (14)	0 (0)	2 (13)
Pain in extremity	0 (0)	0 (0)	2 (29)	0 (0)	2 (13)

n (%)

No deaths were reported, and the incidence of the other serious adverse events was 43% (3 of 7 subjects) in the 300 μg group and 100% (1 of 1 subject) in the 500 μg group. In all of the subjects who received romiplostim, no neutralizing antibodies against romiplostim or TPO were detected.

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Japanese phase II study (Japanese study 20050162, Attached document 5.3.4.2-4, Studied period, February 2006 to November 2006)

An open-label, sequential dose-titration, dose-response exploratory clinical study was conducted at 6 centers in Japan to evaluate the safety and tolerability of romiplostim at the initial dose. In this study, romiplostim 1.0, 3.0, 6.0, or 10.0 μg/kg was subcutaneously administered once weekly to Japanese patients with thrombocytopenia associated with ITP (target sample size, 4 patients per group, 16 patients in total).

During the dose escalation period (for 15 days), romiplostim was subcutaneously administered twice on Days 1 and 8, and the subjects who responded to the study treatment by Day 15 (the

platelet count increased to ≥ twice the baseline level and to ≥50,000/μL) entered the extension period (up to 1 year). The study treatment was started first in the lowest dose group, and proceeding to the next higher dose level of treatment was determined based on the observation until Day 15. The escalation was not to be implemented when any of the following criteria was met until Day 15.

- The platelet count exceeded 450,000/μL in ≥3 of 4 subjects.
- The platelet count exceeded 700,000/μL in ≥2 of 4 subjects.
- The platelet count exceeded 1,000,000/μL in ≥1 of 4 subjects.
- Serious adverse events for which a causal relationship to the study drug could not be ruled out were reported by ≥2 of 4 subjects.

The main inclusion criteria were as follows: Japanese adult chronic ITP patients who had completed at least one type of ITP therapy; and whose mean platelet count over 3 measurements during the screening period was <30,000/μL if they did not receive the ITP therapy during the screening period; or whose mean count was <50,000/μL if they received corticosteroids at a fixed dose. If the patients were *H.pylori*-positive, they had to complete at least 1 course of eradication therapy 12 weeks or more before the initiation of screening.

All of the 12 subjects enrolled in this study (4 subjects each in the 1.0, 3.0, 6.0 μg/kg groups) received the study drug and were included in the safety and efficacy analyses. All of the subjects completed an examination for dose escalation, and then after completing dose escalation period, 5 subjects (1 subject in the 3.0 μg/kg group, 4 subjects in the 6.0 μg/kg group) entered the extension period and completed the study. In 1 subject in the 6.0 μg/kg, the platelet count reached 980,000/μL, or almost 1,000,000/μL, and thus dose escalation to 10.0 μg/kg was canceled.

For the efficacy, the percentage of the subjects who showed a positive platelet response during the dose escalation period was 0.0% (0 of 4 subjects) in the 1.0 μg/kg group, 50.0% (2 of 4 subjects) in the 3.0 μg/kg group, and 100.0% (4 of 4 subjects) in the 6.0 μg/kg group on Day 8, 25.0% (1 of 4 subjects) in the 1.0 μg/kg group, 50.0% (2 of 4 subjects) in the 3.0 μg/kg group, 100.0% (4 of 4 subjects) in the 6.0 μg/kg group on Day 11, 25.0% (1 of 4 subjects) in the 1.0 μg/kg group, 50.0% (2 of 4 subjects) in the 3.0 μg/kg group, 100.0% (4 of 4 subjects) in the 6.0 μg/kg group on Day 15 (for the subjects who entered the extension period, Day 15; for the subjects who did not enter the extension period, Week 1 of the follow-up period). The percentage of the subjects in whom the platelet count increased by ≥20,000/μL from the baseline during the dose escalation period was 50.0% (2 of 4 subjects) in the 1.0 μg/kg group, 75.0% (3 of 4 subjects) in the 3.0 μg/kg group, and 100.0% (4 of 4 subjects) in the 6.0 μg/kg group. The maximum platelet counts (mean ± standard error) during the dose escalation period in the 1.0, 3.0, and 6.0 μg/kg groups were 44,000 ± 24,600, 145,800 ± 80,800, and 374,300 ± 202,100/μL, respectively, with the time to the maximum platelet count being 13.3 ± 1.8, 11.5 ± 1.4, and 14.0 ± 1.0 days, respectively. The changes from the baseline to the maximum platelet count in the 1.0, 3.0, and 6.0 μg/kg groups were 34,250 ± 22,990, 137,000 ± 76,490, and 357,440 ± 199,430/μL, respectively, and the baseline-normalized maximum platelet counts were 4.13 ± 1.64, 15.85 ± 6.28, and 26.23 ± 7.21, respectively.

Based on the above, a positive platelet response was observed on Day 8 in the groups of romiplostim ≥3.0 μg/kg, but the platelet count excessively increased in 1 subject in the 6.0 μg/kg group on Day 15 (7 days after the second dose), suggesting that this dose was inappropriate for the initial dose in Japanese adult chronic ITP patients. Therefore, the initial dose of 3.0 μg/kg of romiplostim was selected for a future Japanese phase III study in Japanese patients with thrombocytopenia associated with ITP.

For the safety, the primary endpoints were the incidences of all adverse events as well as the antibody production, and the incidence of the adverse events during the dose escalation period was 75.0% (3 of 4 subjects) in the 1.0 μg/kg group, 75.0% (3 of 4 subjects) in the 3.0 μg/kg group, and 50.0% (2 of 4 subjects) in the 6.0 μg/kg group. All adverse events reported during the dose escalation period were as shown in Table 3. In any subjects treated with romiplostim, no antibodies binding to romiplostim, TMP of romiplostim, or TPO were detected. During the study period, haemorrhage-related adverse events occurred in 50.0% (2 of 4 subjects) in the 1.0 μg/kg group, 25.0% (1 of 4 subjects) in the 3.0 μg/kg group, and 25.0% (1 of 4 subjects) in the 6.0 μg/kg group, but they were all mild and resolved without treatment, and their causal relationships with the study drug were all ruled out as well.

Table 3. Adverse events reported during the dose escalation period (partially modified from the submitted data)

	Romiplostim (μg/kg)			Total (n = 12)
	1.0 (n = 4)	3.0 (n = 4)	6.0 (n = 4)	
Number of subjects with any adverse event	3 (75.0)	3 (75.0)	2 (50.0)	8 (66.7)
Headache	1 (25.0)	1 (25.0)	1 (25.0)	3 (25.0)
Back pain	1 (25.0)	1 (25.0)	0 (0)	2 (16.7)
Epistaxis	1 (25.0)	1 (25.0)	0 (0)	2 (16.7)
Flushing	0 (0)	0 (0)	1 (25.0)	1 (8.3)
Abdominal distension	0 (0)	1 (25.0)	0 (0)	1 (8.3)
Fatigue	1 (25.0)	0 (0)	0 (0)	1 (8.3)
Flank pain	0 (0)	1 (25.0)	0 (0)	1 (8.3)
Mouth haemorrhage	1 (25.0)	0 (0)	0 (0)	1 (8.3)
Muscle tightness	0 (0)	1 (25.0)	0 (0)	1 (8.3)
Nasopharyngitis	1 (25.0)	0 (0)	0 (0)	1 (8.3)
Prurigo	0 (0)	1 (25.0)	0 (0)	1 (8.3)
Purpura	1 (25.0)	0 (0)	0 (0)	1 (8.3)
Tongue haematoma	1 (25.0)	0 (0)	0 (0)	1 (8.3)

n (%)

There were no deaths, severe adverse events, other serious adverse events, or adverse events leading to study discontinuation.

No clinically significant changes were observed in laboratory values, vital signs, or blood coagulation values during the study period.

4.(iii).A.(2).2) Foreign phase II study (Foreign study 20000137B, Attached document 5.3.4.2-3, Studied period October 2003 to June 2004)

A randomized, double-blind, parallel-group, comparative study was conducted in adult ITP patients at 8 centers in the U.S. to evaluate the safety and tolerability of romiplostim (target sample size; 10 patients per cohort [8 patients in the romiplostim group, 2 patients in the placebo group], 30 patients in total).

In this study, romiplostim 1.0, 3.0, or 6.0 μg/kg or placebo were to be subcutaneously administered once weekly for 6 weeks followed by observation for 6 weeks. The study was designed to consist of 3 cohorts of romiplostim 1.0, 3.0, and 6.0 μg/kg, and in each cohort, subjects were randomized to the romiplostim or placebo groups at the ratio of 4:1.

The main inclusion criteria were as follows: patients who had completed at least one type of ITP therapy; and whose 2 platelet counts measured during the screening period and before dosing were <30,000/μL on average (and ≤35,000/μL each time) if the patients did not receive the ITP

therapy during the screening; or whose counts were <50,000/μL on average (and ≤55,000/μL each time) if the patients regularly received corticosteroids.

Of 10 subjects each assigned to cohorts of 1.0 or 3.0 μg/kg, 8 subjects and 2 subjects received romiplostim and placebo, respectively. One subject was assigned to the cohort of 6.0 μg/kg and received romiplostim, and the platelet count in this subject seemed likely to increase to >500,000/μL. Therefore this cohort was discontinued. All of the subjects assigned to each cohort received the study drug and were included in the safety analysis. In addition, excluding 1 subject in the 6.0 μg/kg group, 20 subjects (8 subjects in the 1.0 μg/kg group, 8 subjects in the 3.0 μg/kg group, 4 subjects in the placebo group) were included in the efficacy analysis. Four subjects in the romiplostim groups and 1 subject in the placebo group discontinued the study treatment due to the increase of the platelet count to >500,000/μL (2 subjects in the 3.0 μg/kg group, 1 subject in the 6.0 μg/kg group), use of prohibited concomitant drugs (1 subject in the 3.0 μg/kg group), and the occurrence of adverse events (1 subject in the placebo group).

At the baseline, 33% of the subjects (7 of 21 subjects) used prednisone concomitantly, and 67% (14 of 21 subjects) were splenectomized.

For the efficacy, the results of the efficacy evaluation based on the maximum platelet count were as shown in Table 4.

Table 4. Efficacy evaluation based on the maximum platelet count (partially modified from the submitted data)

	Placebo (n = 4)	Romiplostim (μg/kg)		
		1.0 (n = 8)	3.0 (n = 8)	Sub-total (n = 16)
Maximum platelet count reached the target range[a]	1 (25)	7 (88)	3 (38)	10 (63)
Platelet count reached twice the baseline count	1 (25)	8 (100)	7 (88)	15 (94)
Platelet count reached 50,000-450,000/μL	2 (50)	7 (88)	3 (38)	10 (63)
Platelet count increased by ≥20,000/μL from the baseline	2 (50)	8 (100)	6 (75)	14 (88)
Maximum platelet count ≥50,000/μL	2 (50)	7 (88)	5 (63)	12 (75)
Maximum platelet count ≥100,000/μL	1 (25)	5 (63)	5 (63)	10 (63)
Maximum platelet count >450,000/μL	0 (0)	0 (0)	2 (25)	2 (13)
Maximum platelet count >500,000/μL	0 (0)	0 (0)	2 (25)	2 (13)

a: Maximum platelet count reached twice the baseline count and the range of 50,000 to 450,000/μL
n (%)

The maximum platelet count in the 1.0, 3.0 μg/kg, and placebo groups were 134,500 ± 90,200 (mean ± SD), 240,900 ± 288,300, and 80,800 ± 96,000/μL, respectively. The median time to the maximum platelet count estimated by the Kaplan-Meier method in the respective groups above was 18, 19, and 63 days. The maximum platelet count in this study was 822,000/μL in the 3.0 μg/kg group. The platelet count changes from the baseline and their baseline-normalized changes were as shown in Table 5.

Table 5. Changes in platelet count from baseline and baseline-normalized changes (partially modified from the submitted data)

	Placebo (n = 4)	Romiplostim (μg/kg)		
		1.0 (n = 8)	3.0 (n = 8)	Sub-total (n = 16)
Change from the baseline (/μL)				
Number of subjects	4	8	8	16
Mean	52,400	117,600	226,900	172,300
SD	92,900	88,300	284,100	210,900
Median	10,900	99,500	100,000	100,000
Q1, Q3	-1,600, 106,400	49,200, 166,500	20,700, 382,000	32,200, 231,000
Minimum, maximum	-3,000, 191,000	22,000, 289,000	10,000, 800,000	10,000, 800,000
Baseline-normalized change				
Number of subjects	4	8	8	16
Mean	2.7	8.5	17.0	12.7
SD	3.1	4.8	18.9	14.0
Median	1.4	7.2	7.6	7.4
Q1, Q3	0.8, 4.6	5.0, 11.9	3.1, 30.0	4.0, 15.4
Minimum, maximum	1, 7	3, 17	2, 53	2, 53

The results of this study suggested that it is appropriate for the future studies of romiplostim in ITP patients to start the study treatment at 1.0 μg/kg once weekly and then adjust the dose individually.

For the safety, the primary endpoints were the incidences and severities of all adverse events as well as the antibody production. The incidences of the adverse events were 100.0% in all groups. The adverse events reported by ≥10% of subjects were as shown in Table 6. The severe adverse events occurred in 1 subject in the 1.0 μg/kg group (13%), 3 subjects in the 3.0 μg/kg group (38%), and 2 subjects in the placebo group (50%).

Table 6. Adverse events reported by ≥10% of subjects (partially modified from the submitted data)

MedDRA ver 8.0 PT	Placebo (n = 4)	Romiplostim (μg/kg)			
		1.0 (n = 8)	3.0 (n = 8)	6.0 (n = 1)	Sub-total (n = 17)
Number of subjects with any adverse event	4 (100)	8 (100)	8 (100)	1 (100)	17 (100)
Contusion	2 (50)	6 (75)	3 (38)	0 (0)	9 (53)
Epistaxis	2 (50)	3 (38)	4 (50)	0 (0)	7 (41)
Headache	0 (0)	2 (25)	3 (38)	0 (0)	5 (29)
Oral mucosal blistering	0 (0)	1 (13)	3 (38)	1 (100)	5 (29)
Ecchymosis	2 (50)	3 (38)	1 (13)	0 (0)	4 (24)
Gingival bleeding	1 (25)	0 (0)	4 (50)	0 (0)	4 (24)
Petechiae	1 (25)	3 (38)	1 (13)	0 (0)	4 (24)
Diarrhoea	1 (25)	0 (0)	2 (25)	1 (100)	3 (18)
Excoriation	0 (0)	1 (13)	2 (25)	0 (0)	3 (18)
Purpura	0 (0)	1 (13)	2 (25)	0 (0)	3 (18)
Thrombocytopenia	0 (0)	1 (13)	2 (25)	0 (0)	3 (18)
Upper respiratory tract infection	1 (25)	0 (0)	3 (38)	0 (0)	3 (18)
Abdominal pain	1 (25)	1 (13)	1 (13)	0 (0)	2 (12)
Dizziness	1 (25)	0 (0)	2 (25)	0 (0)	2 (12)
Erythema	0 (0)	1 (13)	1 (13)	0 (0)	2 (12)
Flushing	0 (0)	0 (0)	2 (25)	0 (0)	2 (12)
Haematochezia	0 (0)	2 (25)	0 (0)	0 (0)	2 (12)
Herpes simplex	0 (0)	0 (0)	2 (25)	0 (0)	2 (12)
Insomnia	0 (0)	1 (13)	1 (13)	0 (0)	2 (12)
Muscle cramp	0 (0)	2 (25)	0 (0)	0 (0)	2 (12)
Nausea	1 (25)	0 (0)	2 (25)	0 (0)	2 (12)
Rash erythematous	0 (0)	1 (13)	1 (13)	0 (0)	2 (12)
Stomatitis	2 (50)	1 (13)	1 (13)	0 (0)	2 (12)
Venipuncture site contusion	0 (0)	0 (0)	2 (25)	0 (0)	2 (12)

n (%)

Neither deaths nor adverse events leading to study discontinuation were reported, but other serious adverse events were reported by 1 subject in the 3.0 μg/kg (contusion/rectal haemorrhage/thrombocytopenia/vaginal haemorrhage) and by 2 subjects in the placebo group (asthma, deep vein thrombosis/haemorrhage intracranial). A causal relationship to the study drug was not ruled out for the events in the 3.0 μg/kg group.

In any subjects treated with the study drug, no neutralizing antibodies against romiplostim or TPO were detected.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Japanese phase III study (Japanese study 20[redacted]0216, Attached document 5.3.5.1-3, Studied period [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, comparative study was conducted at 11 centers in Japan to evaluate the efficacy and safety of romiplostim. In this study, romiplostim or placebo was to be subcutaneously administered once weekly to Japanese patients with thrombocytopenia associated with ITP (target sample size; 20 patients in the romiplostim group, 10 patients in the placebo group, 30 patients in total).

The study treatment was started with a subcutaneous dose of romiplostim 3.0 μg/kg or placebo once weekly and continued for 12 weeks with dose adjustments according to the rules shown in Table 7 to maintain the platelet count at 50,000/μL to 200,000/μL. The maximum dose of romiplostim was set at 10 μg/kg.

Table 7. Dose adjustment rules (partially modified from the submitted data)

Platelet count (/μL)	Dose adjustment
<10,000	Increase dose by 1 μg/kg.
≥10,000 and <50,000	Increase dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (increase biweekly).
≥50,000 and ≤200,000	Continue the same dose.
>200,000 and ≤400,000	Decrease dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (decrease biweekly).
>400,000	Hold the scheduled dose on the day, and resume the treatment at the dose decreased by 1 μg/kg on the next or later scheduled treatment day if the platelet count has decreased to ≤200,000/μL.

When the dose has to be decreased during the study treatment with romiplostim 1.0 μg/kg, treatment should be discontinued until the platelet count decreases to <50,000/μL and then the treatment should be resumed at the dose of romiplostim 1.0 μg/kg.

The main inclusion criteria were as follows: adult chronic ITP patients who had had a diagnosis of ITP 6 months or more before and completed at least one type of ITP therapy; and whose mean platelet count over 3 measurements during the screening period was ≤30,000/μL with each count ≤35,000/μL. If the patients were *H.pylori*-positive, they had to complete at least 1 course of eradication therapy 12 weeks or more before the initiation of screening. Patients were stratified by splenectomy status at randomization (romiplostim:placebo = 2:1).

All of the 34 patients enrolled (22 patients in the romiplostim group, 12 patients in the placebo group) received the study drug, completed the study, and were included in the safety and efficacy analyses.

As for the background of the subjects enrolled in this study, the percentage of the subjects who concomitantly received the ITP therapy at the baseline was 59.1% (13 of 22 subjects) in the romiplostim group and 83.3% (10 of 12 subjects) in the placebo group. That of the splenectomized subjects was 45.5% (10 of 22 subjects) and 41.7% (5 of 12 subjects), that of the subjects who had undergone *H.pylori* eradication therapy was 50.0% (11 of 22 subjects) and 25.0% (3 of 12 subjects), and all of the subjects had received corticosteroids as a part of the ITP therapy. The platelet counts (mean ± SD) at the baseline in the romiplostim group and placebo group were 18,400 ± 8300 and 15,800 ± 8600/μL, respectively.

For the efficacy, the number of weeks (median, [first quartile, third quartile]) in which a positive platelet response (the platelet count being increased to ≥50,000/μL, measured on the scheduled day of each week between Weeks 2 and 13[*]) was observed, the primary endpoint, was 11.0 (9.0, 12.0) weeks in the romiplostim group and 0 (0.0, 0.0) weeks in the placebo group; the number in the romiplostim group was significantly greater than that in the placebo group ($P < 0.0001$, Wilcoxon rank sum test). The percentage of the subjects with a positive platelet response during the treatment period was as shown in Figure 6.

* In the cases where salvage therapy was implemented to increase the platelet count, data during the 4 weeks after such therapy were excluded from the evaluation.

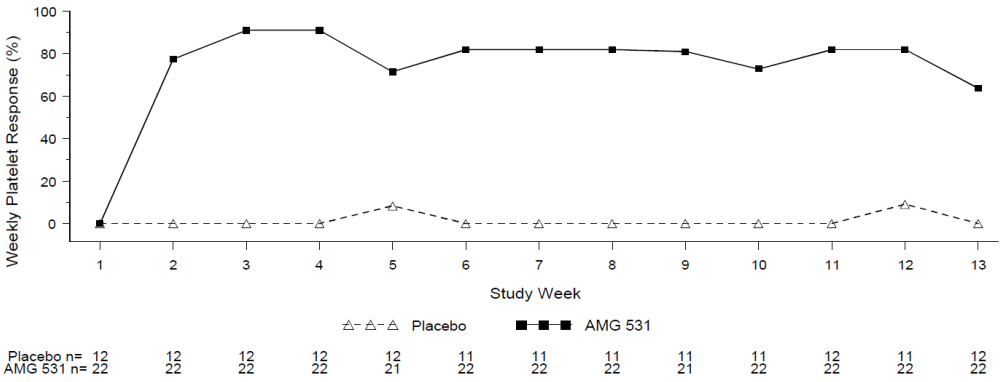


Figure 6. Percentage of subjects with a positive platelet response over time (partially modified from the submitted data)

Major results on the secondary efficacy endpoints are described below. The percentage of the subjects with a platelet count increased by ≥20,000/μL from the baseline was 95.5% (21 of 22 subjects) in the romiplostim group and 25.0% (3 of 12 subjects) in the placebo group. The mean change in the platelet count from the baseline to the scheduled day of each week (mean ± SD) during the last 4 weeks of the treatment period (Weeks 10-13) was 109,700 ± 88,500/μL in the romiplostim group and 2300 ± 6500/μL in the placebo group. The number of weeks in which a positive platelet response was observed (mean ± SD) (in this study, defined as the platelet count being increased to ≥50,000/μL and ≤200,000/μL, measured on the scheduled day of each week between Weeks 2 and 13) was 6.3 ± 3.2 weeks in the romiplostim group and 0.2 ± 0.4 weeks in the placebo group. The percentage of the subjects who received the salvage therapy to increase the platelet count was 9.1% (2 of 22 subjects) in the romiplostim group and 16.7% (2 of 12 subjects) in the placebo group.

For the safety, the incidence of adverse events was 90.9% (20 of 22 subjects) in the romiplostim group and 91.7% (11 of 12 subjects) in the placebo group. The adverse events reported by ≥2 subjects in the romiplostim and placebo groups were as shown in Table 8.

Table 8. Adverse events reported by ≥2 subjects (partially modified from the submitted data)

MedDRA ver 12.0 PT	Placebo (n = 12)	Romiplostim (n = 22)
Number of subjects with any adverse event	11 (92)	20 (91)
Nasopharyngitis	2 (17)	9 (41)
Headache	2 (17)	7 (32)
Oedema peripheral	0 (0)	4 (18)
Back pain	0 (0)	3 (14)
Pain in extremity	0 (0)	3 (14)
Arthralgia	1 (8)	2 (9)
Fatigue	0 (0)	2 (9)
Nephrocalcinosis	0 (0)	2 (9)
Thermal burn	0 (0)	2 (9)
Thrombocytopenia	0 (0)	2 (9)
Malaise	2 (17)	1 (5)
Bronchitis	1 (8)	1 (5)
Diarrhoea	1 (8)	1 (5)
Eczema	1 (8)	1 (5)
Gastrointestinal haemorrhage	1 (8)	1 (5)
Iron deficiency anaemia	1 (8)	1 (5)
Petechiae	1 (8)	1 (5)
Subarachnoid haemorrhage	1 (8)	1 (5)
Urticaria	1 (8)	1 (5)
Contusion	2 (17)	0 (0)

n (%)

Neither deaths nor adverse events leading to study discontinuation were reported. Other serious adverse events occurred in 2 subjects in the romiplostim group (thrombocytopenia and subarachnoid haemorrhage, 1 subject each) and in 1 subject in the placebo group (gastrointestinal haemorrhage/cerebral haemorrhage/subarachnoid haemorrhage), but a causal relationship to the study drug was ruled out for all the events.

In 3 subjects in the romiplostim group, antibodies binding to romiplostim and the peptide moiety of romiplostim were positive at the baseline. In these subjects, the platelet count increased without problematic adverse events. After the initiation of the study treatment, no other subjects were tested positive for antibodies binding to romiplostim or TMP of romiplostim, or neutralizing antibodies.

4.(iii).A.(3).2) Foreign study 20030105 (Attached document 5.3.5.1-1, Studied period March 2005 to September 2006)

A randomized, double-blind, comparative study was conducted at a total of 32 centers in the U.S., the UK, France, the Netherlands, or Spain to evaluate the efficacy and safety of romiplostim in splenectomized patients with thrombocytopenia associated with ITP. In this study, romiplostim 1.0 μg/kg or placebo was subcutaneously administered once weekly to splenectomized adult ITP patients (target sample size: 40 patients in the romiplostim group; 20 patients in the placebo group; 60 patients in total).

The study treatment was started with a subcutaneous dose of romiplostim 1.0 μg/kg or placebo once weekly and continued for 24 weeks with dose adjustments to maintain the platelet count at 50,000/μL to 200,000/μL according to the dose adjustment rules shown in Table 9. The maximum dose of romiplostim was set at 15 μg/kg. After the study treatment, observation was to be continued until Week 36 and discontinued when the platelet count decreased to ≤50,000/μL.

Table 9. Dose adjustment rules (partially modified from the submitted data)

Platelet count (/μL)	Dose adjustment
Start-up period (until the platelet count increases to >50,000/μL)	
≤10,000	Increase dose by 2 μg/kg weekly.
>10,000 and ≤50,000	Increase dose by 2 μg/kg after 2 consecutive platelet counts are ≤50,000/μL (increase biweekly).
>50,000	Continue the same dose in accordance with the following adjustment rules.
Maintenance period (after the platelet count increases to >50,000/μL at least once)	
≤10,000	Increase dose by 1 μg/kg weekly.
>10,000 and ≤50,000	Increase dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (increase biweekly).
>50,000 and ≤200,000	Continue the same dose.
>200,000 and ≤400,000	Decrease dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (decrease biweekly).
>400,000	Hold the next scheduled dose, and resume the treatment at the dose decreased by 1 μg/kg if the platelet count has decreased to ≤200,000/μL.

When the dose has to be decreased during the study treatment with romiplostim 1.0 μg/kg, treatment should be discontinued until the platelet count decreases to ≤50,000/μL and then the treatment should be resumed at the dose of romiplostim 1.0 μg/kg.

The main inclusion criteria were as follows: adult ITP patients who underwent splenectomy 4 weeks or more before the study participation; and whose mean platelet count over 3 measurements during the screening period and before dosing was ≤30,000/μL with each count ≤35,000/μL. Patients were stratified by the concomitant ITP therapy at the baseline at randomization (romiplostim:placebo = 2:1).

All of the 63 subjects enrolled (42 subjects in the romiplostim group, 21 subjects in the placebo group) received the study drug and were included in the safety and efficacy analyses. Two subjects (4.8%) in the romiplostim group and 12 subjects (57.1%) in the placebo group discontinued the study treatment due to death (1 subject in the placebo group); the occurrence of adverse events for which a causal relationship to the study drug could not be ruled out (2 subjects in the romiplostim group); request from the subjects (6 subjects in the placebo group); and other reasons (5 subjects in the placebo group).

As for the background of the subjects included in this study, the percentage of the subjects who concomitantly received the ITP therapy at the baseline was 33% (14 of 42 subjects) in the romiplostim group and 33% (7 of 21 subjects) in the placebo group, the number of years from the splenectomy to the baseline point (median [range]) was 5.83 years (0.2-43.0 years) and 8.08 years (0.9-31.4 years), and the platelet count at baseline (median [range]) was 13,500/μL (3000-29,000/μL) and 14,700/μL (2000-28,000/μL), respectively.

The percentage of the subjects with the durable platelet response (platelet response without the salvage therapy continued for 6 weeks or longer of the last 8 weeks during the study period [Weeks 18-25], [in this study, defined as the platelet count being ≥50,000/μL based on the platelet counts measured in Weeks 2-25]), the primary efficacy endpoint, was 38.1% (16 of 42 subjects) in the romiplostim group and 0% in the placebo group; the percentage in the romiplostim group was significantly greater than that in the placebo group (P = 0.0013, Cochran-Mantel-Haenszel test after stratification by concomitant ITP therapy at the baseline).

Major results on the secondary efficacy endpoints are described below. The percentage of the subjects who achieved either a durable or transient platelet response (a transient platelet response is defined as ≥4 positive responses being observed during the treatment period in Weeks 2-25 without a durable platelet response) was 78.6% (33 of 42 subjects) in the romiplostim group and 0% in the placebo group and positive response period (mean ± SD) was 12.3 ± 7.9 and 0.2 ± 0.5

weeks, respectively. The percentage of the subjects who received the salvage therapy to increase the platelet count was 26.2% (11 of 42 subjects) in the romiplostim group and 57.1% (12 of 21 subjects) in the placebo group. The percentage of the subjects with a durable positive platelet response at a fixed dose (dose changes during the last 8 weeks of the treatment period fall within ± 1 μg/kg) was 31.0% (13 of 42 subjects) in the romiplostim group and 0% in the placebo group. Platelet counts (median) over time in the romiplostim and placebo groups were as shown in Figure 7.

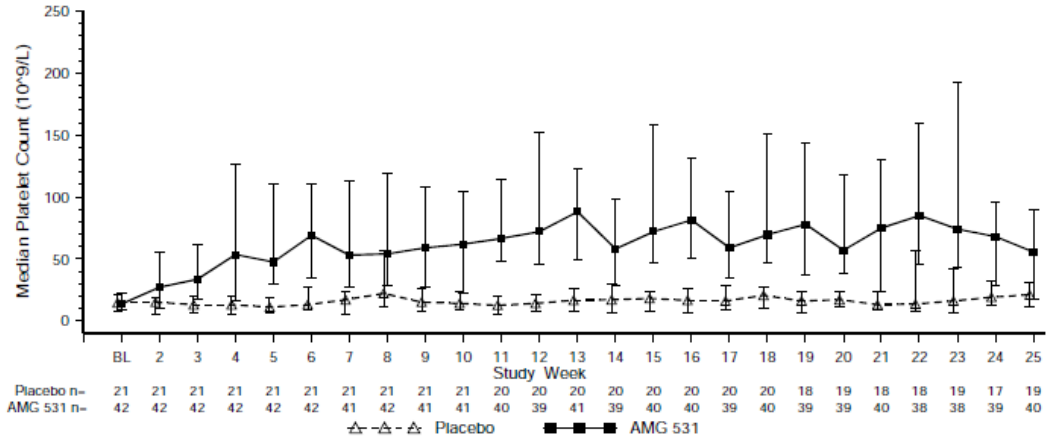


Figure 7. Platelet counts over time (median [first quartile, third quartile]) (partially modified from the submitted data)

The incidence of adverse events was 100.0% (42 of 42 subjects) in the romiplostim group and 95.2% (20 of 21 subjects) in the placebo group, and adverse events reported by ≥2 subjects in any group were as shown in Table 10.

Table 10. Adverse events reported by ≥2 subjects in any group (partially modified from the submitted data)

MedDRA ver 9.0 PT	Placebo (n = 21)	Romiplostim (n = 42)	MedDRA ver 9.0 PT	Placebo (n = 21)	Romiplostim (n = 42)
Number of subjects with any adverse event	20 (95.2)	42 (100.0)	Rhinitis allergic	0 (0)	3 (7.1)
Headache	7 (33.3)	18 (42.9)	Viral upper respiratory tract infection	0 (0)	3 (7.1)
Epistaxis	7 (33.3)	16 (38.1)	Weight increased	0 (0)	3 (7.1)
Fatigue	5 (23.8)	13 (31.0)	Rash	2 (9.5)	2 (4.8)
Arthralgia	3 (14.3)	12 (28.6)	Sinusitis	2 (9.5)	2 (4.8)
Diarrhoea	2 (9.5)	9 (21.4)	Anaemia	1 (4.8)	2 (4.8)
Myalgia	0 (0)	9 (21.4)	Blood blister	1 (4.8)	2 (4.8)
Contusion	3 (14.3)	8 (19.0)	Depression	1 (4.8)	2 (4.8)
Upper respiratory tract infection	3 (14.3)	8 (19.0)	Dyspnoea	1 (4.8)	2 (4.8)
Insomnia	1 (4.8)	8 (19.0)	Dyspnoea exertional	1 (4.8)	2 (4.8)
Petechiae	5 (23.8)	7 (16.7)	Platelet count decreased	1 (4.8)	2 (4.8)
Cough	3 (14.3)	7 (16.7)	Tooth abscess	1 (4.8)	2 (4.8)
Dizziness	0 (0)	7 (16.7)	Abdominal pain upper	0 (0)	2 (4.8)
Pain	2 (9.5)	6 (14.3)	Acne	0 (0)	2 (4.8)
Pharyngolaryngeal pain	0 (0)	6 (14.3)	Angina pectoris	0 (0)	2 (4.8)
Pyrexia	0 (0)	6 (14.3)	Blood pressure increased	0 (0)	2 (4.8)
Back pain	3 (14.3)	5 (11.9)	Bone pain	0 (0)	2 (4.8)
Muscle spasms	2 (9.5)	5 (11.9)	Bronchitis	0 (0)	2 (4.8)
Nausea	2 (9.5)	5 (11.9)	Candidiasis	0 (0)	2 (4.8)
Oedema peripheral	2 (9.5)	5 (11.9)	Flushing	0 (0)	2 (4.8)
Oral mucosal blistering	2 (9.5)	5 (11.9)	Haematochezia	0 (0)	2 (4.8)
Asthenia	1 (4.8)	5 (11.9)	Haemoptysis	0 (0)	2 (4.8)
Ecchymosis	4 (19.0)	4 (9.5)	Hot flush	0 (0)	2 (4.8)
Gingival bleeding	4 (19.0)	4 (9.5)	Lacrimation increased	0 (0)	2 (4.8)
Anxiety	3 (14.3)	4 (9.5)	Menorrhagia	0 (0)	2 (4.8)
Nasopharyngitis	2 (9.5)	4 (9.5)	Metrorrhagia	0 (0)	2 (4.8)
Injection site pain	1 (4.8)	4 (9.5)	Migraine	0 (0)	2 (4.8)
Vomiting	1 (4.8)	4 (9.5)	Muscular weakness	0 (0)	2 (4.8)
Abdominal pain	0 (0)	4 (9.5)	Nasal congestion	0 (0)	2 (4.8)
Dyspepsia	0 (0)	4 (9.5)	Oedema	0 (0)	2 (4.8)
Haematoma	0 (0)	4 (9.5)	Shoulder pain	0 (0)	2 (4.8)
Oral mucosal petechiae	2 (9.5)	3 (7.1)	Skin haemorrhage	0 (0)	2 (4.8)
Alopecia	1 (4.8)	3 (7.1)	Sleep apnoea syndrome	0 (0)	2 (4.8)
Influenza	1 (4.8)	3 (7.1)	Thrombocytopenia	0 (0)	2 (4.8)
Injection site bruising	1 (4.8)	3 (7.1)	Hypertension	2 (9.5)	1 (2.4)
Chills	0 (0)	3 (7.1)	Neck pain	2 (9.5)	1 (2.4)
Musculoskeletal chest pain	0 (0)	3 (7.1)	Pruritus	2 (9.5)	1 (2.4)
Pain in extremity	0 (0)	3 (7.1)	Vision blurred	2 (9.5)	1 (2.4)
Paraesthesia	0 (0)	3 (7.1)			

n (%)

Adverse events resulting in deaths were reported by 3 subjects in the placebo group (cerebral haemorrhage, pneumonia primary atypical, pulmonary embolism), but a causal relationship to the study drug was ruled out for all the events. Serious adverse events were reported by 9 subjects in the romiplostim group and by 5 subjects in the placebo group. They include platelet count decreased (1 subject in the romiplostim group, 1 subject in the placebo group), bone marrow disorder, idiopathic thrombocytopenic purpura, thrombocytopenia, gastrointestinal haemorrhage, haematochezia, oral mucosal petechiae, hypersensitivity, appendicitis, hypovolaemia, suicide attempt, angioneurotic oedema, ecchymosis, hypertension, peripheral embolism, peripheral ischaemia (1 subject each in the romiplostim group), pneumonia (2 subjects in the placebo group), gastric haemorrhage, Evans syndrome, pneumonia primary atypical, cerebral haemorrhage, haemorrhage intracranial, headache, pulmonary embolism, and purpura (1 subject each in the

placebo group). A causal relationship to the study drug could not be ruled out for bone marrow disorder, peripheral embolism, or peripheral ischaemia in the romiplostim group. Adverse events leading to study drug discontinuation were reported by 2 subjects in the romiplostim group (arthralgia, bone marrow disorder and myalgia). Of these, 1 subject with bone marrow disorder was discontinued from the study. However, a causal relationship to the study drug could not be ruled out for any of the events. In the subject who was discontinued from the study, bone marrow reticulin fibrosis was observed at the time of study participation. After the initiation of romiplostim treatment, a positive platelet response was not observed, but bone marrow reticulin increased. Collagen did not increase, and after the discontinuation of the study, reticulin increased resolved. As thrombosis/thromboembolism-related adverse events, pulmonary embolism occurred in 1 of 21 subjects (4.8%) in the placebo group, and peripheral embolism occurred in 1 of 42 subjects (2.4%) in the romiplostim group.

At the baseline (before the study treatment), 5 subjects were tested positive for antibodies binding to romiplostim or romiplostim TMP, and 4 subjects were positive for antibodies binding to TPO. Of these, 1 subject tested positive for antibodies binding to romiplostim at the baseline became negative for any type of antibodies tested after dosing. One subject tested positive for antibodies binding to TPO also had antibodies neutralizing TPO. This subject was also tested positive for antibodies binding to TPO at the end of the study treatment, but negative for antibodies neutralizing TPO. The negative result was also obtained for all types of antibodies on the other days of the test. For others, 6 subjects tested positive for binding antibodies at the baseline remained positive even after the initiation of the study treatment. Of the subjects tested negative for binding antibodies at the baseline, 2 subjects became positive for antibodies binding to romiplostim and 1 subject became positive for antibodies binding to TPO after the initiation of the study treatment, but all of them were tested negative for neutralizing antibodies.

4.(iii).A.(3).3) Foreign study 20030212 (Attached document 5.3.5.1-2, Studied period April 2005 to December 2006)

A randomized, double-blind, comparative study was conducted at a total of 25 centers in the U.S., the UK, France, the Netherlands, or Spain to evaluate the efficacy and safety of romiplostim. In this study, romiplostim or placebo was subcutaneously administered once weekly to non-splenectomized adult ITP patients (target sample size, 60 patients in total: 40 patients in the romiplostim group; 20 patients in the placebo group,).

The study treatment was started with a subcutaneous administration of romiplostim 1.0 μg/kg or placebo once weekly and continued for 24 weeks with dose adjustments to maintain the platelet count at 50,000/μL to 200,000/μL according to the dose adjustment rules shown in Table 11. The maximum dose of romiplostim was set at 15 μg/kg. After the study treatment, observation was to be continued until Week 36 and discontinued when the platelet count decreased to ≤50,000/μL.

Table 11. Dose adjustment rules (partially modified from the submitted data)

Platelet count (/μL)	Dose adjustment
Start-up period (until the platelet count increases to >50,000/μL)	
≤10,000	Increase dose by 2 μg/kg weekly.
>10,000 and ≤50,000	Increase dose by 2 μg/kg after 2 consecutive platelet counts are ≤50,000/μL (increase biweekly).
>50,000	Continue the same dose in accordance with the following adjustment rules.
Maintenance period (after the platelet count increases to >50,000/μL at least once)	
≤10,000	Increase dose by 1 μg/kg weekly.
>10,000 and ≤50,000	Increase dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (increase biweekly).
>50,000 and ≤200,000	Continue the same dose.
>200,000 and ≤400,000	Decrease dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (decrease biweekly).
>400,000	Hold the next scheduled dose, and resume the treatment at the dose decreased by 1 μg/kg if the platelet count has decreased to ≤200,000/μL.

When the dose has to be decreased during the study treatment with romiplostim 1.0 μg/kg, treatment should be discontinued until the platelet count decreases to ≤50,000/μL and then the treatment should be resumed at the dose of romiplostim 1.0 μg/kg.

The main inclusion criteria were as follows: non-splenectomized adult ITP patients who had completed at least one type of ITP therapy; and whose mean platelet count over 3 measurements during the screening period and before dosing was ≤30,000/μL with each count ≤35,000/μL. Patients were stratified by the concomitant ITP therapy at the baseline at randomization (romiplostim:placebo = 2:1).

All of the 62 subjects enrolled (41 subjects in the romiplostim group, 21 subjects in the placebo group) received the study drug and were included in the safety and efficacy analyses. One subject allocated to the placebo group received 3 doses of romiplostim by mistake. This subject was included in the placebo group for the efficacy analysis but in the romiplostim group for the safety analysis. Three subjects (7.3%) in the romiplostim group and 8 subjects (38.1%) in the placebo group discontinued the study treatment mainly due to the occurrence of adverse events (2 subjects, 1 subject, respectively), consent withdrawal (2 subjects in the placebo group), and request from the subjects (1 subject each).

As for the background of the subjects enrolled in this study, 16 subjects in the romiplostim group and 8 subjects in the placebo group concomitantly had received the ITP therapy at the baseline, and the platelet count at baseline (median [range]) was 18,700/μL (2000-29,000/μL) and 19,300/μL (5000-31,000/μL), respectively. All of the subjects enrolled had a history of ITP treatment.

The percentage of the subjects with the durable platelet response (platelet response without the salvage therapy continued for 6 weeks or longer of the last 8 weeks during the study period [Weeks 18-25], [in this study, defined as the platelet count being ≥50,000/μL based on the platelet counts measured in Weeks 2-25]), the primary efficacy endpoint, was 61.0% (25 of 41 subjects) in the romiplostim group and 4.8% (1 of 21 subjects) in the placebo group; the percentage in the romiplostim group was significantly greater than that in the placebo group ($P <$ 0.0001, Cochran-Mantel-Haenszel test after stratification by concomitant ITP therapy at the baseline).

Major results on the secondary efficacy endpoints are described below. The percentage of the subjects who achieved either a durable or transient platelet response (a transient platelet response is defined as ≥4 positive responses being observed during the treatment period in Weeks 2-25 without a durable platelet response) was 87.8% (36 of 41 subjects) in the romiplostim group and

14.3% (3 of 21 subjects) in the placebo group. The positive response period (mean ± SD) was 15.2 ± 7.5 weeks in the romiplostim group and 1.3 ± 3.5 weeks in the placebo group. The percentage of the subjects who had the salvage therapy to increase the platelet count was 17.1% (7 of 41 subjects) and 61.9% (13 of 21 subjects) in the respective groups above. The percentage of the subjects with a durable platelet response at a fixed dose (dose changes during the last 8 weeks of the treatment period fall within ± 1 μg/kg) was 51.2% (21 of 41 subjects) and 0% in the respective groups above. Platelet counts (median) over time in the study were as shown in Figure 8.

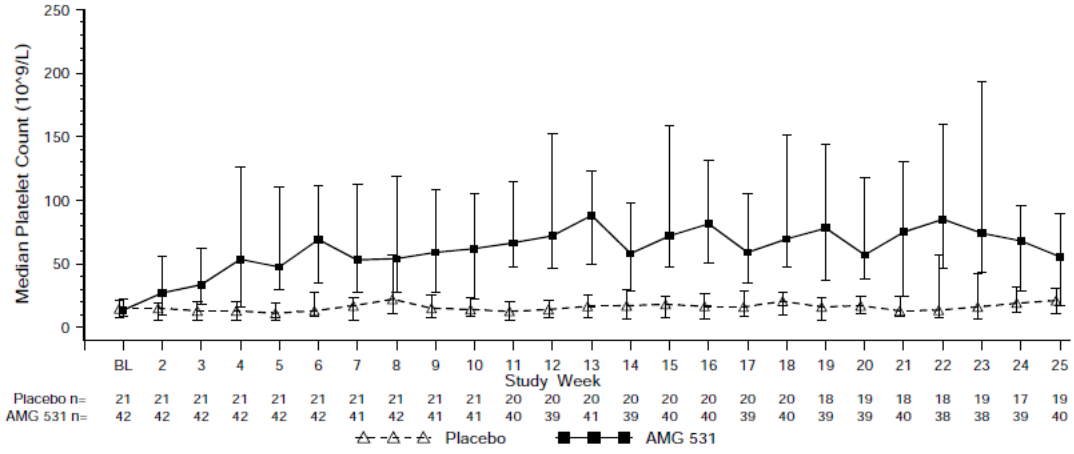


Figure 8. Platelet counts over time (median [first quartile, third quartile]) (FAS) (partially modified from the submitted data)

The incidence of adverse events was 100% (42 of 42 subjects) in the romiplostim group and 95.0% (19 of 20 subjects) in the placebo group, and adverse events reported by ≥2 subjects in any group were as shown in Table 12.

Table 12. Adverse events reported by ≥2 subjects in any group (partially modified from the submitted data)

MedDRA ver 9.0 PT	Placebo (n = 20)	Romiplostim (n = 42)	MedDRA ver 9.0 PT	Placebo (n = 21)	Romiplostim (n = 42)
Number of subjects with any adverse event	19 (95.0)	42 (100.0)	Rash	2 (10.0)	3 (7.1)
Fatigue	7 (35.0)	15 (35.7)	Urinary tract infection	2 (10.0)	3 (7.1)
Contusion	7 (35.0)	13 (31.0)	Myalgia	1 (5.0)	3 (7.1)
Headache	6 (30.0)	11 (26.2)	Anaemia	0 (0)	3 (7.1)
Epistaxis	3 (15.0)	11 (26.2)	Excoriation	0 (0)	3 (7.1)
Arthralgia	5 (25.0)	10 (23.8)	Pruritus	0 (0)	3 (7.1)
Pain in extremity	2 (10.0)	8 (19.0)	Ecchymosis	2 (10.0)	2 (4.8)
Petechiae	4 (20.0)	7 (16.7)	Hyperhidrosis	2 (10.0)	2 (4.8)
Dizziness	0 (0)	7 (16.7)	Dyspnoea	1 (5.0)	2 (4.8)
Nausea	2 (10.0)	6 (14.3)	Haematoma	1 (5.0)	2 (4.8)
Upper respiratory tract infection	2 (10.0)	6 (14.3)	Oral mucosal blistering	1 (5.0)	2 (4.8)
Back pain	1 (5.0)	6 (14.3)	Depression	0 (0)	2 (4.8)
Diarrhoea	4 (20.0)	5 (11.9)	Dysarthria	0 (0)	2 (4.8)
Anxiety	2 (10.0)	5 (11.9)	Dyspepsia	0 (0)	2 (4.8)
Insomnia	2 (10.0)	5 (11.9)	Meteorism	0 (0)	2 (4.8)
Gingival bleeding	1 (5.0)	5 (11.9)	Herpes simplex	0 (0)	2 (4.8)
Injection site bruising	1 (5.0)	5 (11.9)	Hydronephrosis	0 (0)	2 (4.8)
Abdominal pain	0 (0)	5 (11.9)	Paraesthesia	0 (0)	2 (4.8)
Shoulder pain	0 (0)	5 (11.9)	Splenomegaly	0 (0)	2 (4.8)
Nasopharyngitis	5 (25.0)	3 (7.1)	Abdominal pain upper	2 (10.0)	1 (2.4)
Cough	4 (20.0)	3 (7.1)	Haematuria	2 (10.0)	1 (2.4)
Chest discomfort	2 (10.0)	3 (7.1)	Pharyngolaryngeal pain	2 (10.0)	1 (2.4)
Muscle spasms	2 (10.0)	3 (7.1)			

n (%)

An adverse event resulting in death was reported by 1 subject in the romiplostim group (haemorrhage intracranial), but its causal relationship to the study drug was ruled out. Serious adverse events were reported by 5 subjects in the romiplostim group and 3 subjects in the placebo group. They include pericardial effusion, gastrointestinal haemorrhage, head injury, road traffic accident, sternal fracture, B-cell lymphoma, cerebrovascular accident, haemorrhage intracranial, and epistaxis (1 subject each in the romiplostim group), and autoimmune haemolytic anaemia, platelets decreased, and petechiae (1 subject each in the placebo group). However, a causal relationship to the study drug was ruled out for all the events.

Adverse events leading to study drug discontinuation were reported by 2 subjects in the romiplostim group (B-cell lymphoma, haemorrhage intracranial) and 1 subject in the placebo group (metastases to liver), which resulted in discontinuation of the study. A causal relationship to the study drug was ruled out for all the events. Thrombosis/thromboembolism-related adverse events were reported by 1 subject (2.4%) in the romiplostim group. In that subject, cerebrovascular accident occurred 3 days after the 21st dose of romiplostim. The platelet count at that time was 107,000/μL. After occurrence of cerebrovascular accident, this subject received antiplatelet and antihypertensive drugs but died due to haemorrhage intracranial.

After the initiation of the study treatment, 4 of 62 subjects were tested positive for antibodies binding to romiplostim and 5 of 62 subjects for antibodies binding to TPO, but all of the subjects were tested negative for neutralizing antibodies.

4.(iii).A.(4) Long-term extension studies

4.(iii).A.(4).1) Japanese long-term extension study (Japanese study 20[redacted]0113, Attached document 5.3.5.2-2, Studied period [redacted] 20[redacted] to ongoing [data cutoff, [redacted], 20[redacted]; database snapshot, [redacted], 20[redacted]])

An open-label, long-term extension study was conducted at 13 centers in Japan to evaluate the safety and efficacy of a long-term extension treatment with romiplostim. In this study, romiplostim was subcutaneously administered once weekly to Japanese chronic ITP patients who had completed Studies 20050162 and 20[redacted]0216.

The study treatment was started at the final dose level of the previous study for the subjects who were enrolled within 12 weeks after the last dosing of the study drug in the previous study and in whom the platelet count increased by ≥20,000/μL from the baseline during the treatment period of the previous study (except for the 4 weeks after salvage therapy). On the other hand, the study treatment was started with a dose of romiplostim 3.0 μg/kg for subjects who were enrolled >12 weeks after the last dosing of the study drug of the previous study or in whom the platelet count did not increase by ≥20,000/μL from the baseline at any time point during the treatment period of the previous study. In these studies, romiplostim was subcutaneously administered once weekly, and then the dose was adjusted in accordance with the dose adjustment rules in Table 13-1). The dose adjustment rules were changed to those shown in Table 13-2) on [redacted], 20[redacted]. The maximum dose was set at 10 μg/kg. The subjects with 4 consecutive platelet counts ≤20,000/μL in spite of treatment with romiplostim 10 μg/kg were to discontinue the study and be subjected to follow-up. However, the investigator etc., decided whether or not to continue the treatment according to individual conditions and status if the treatment with romiplostim was considered useful for the subject. When the dose had to be decreased during the study treatment of romiplostim 1.0 μg/kg, treatment should be discontinued until the platelet count decreases to <50,000/μL and then the treatment should be resumed at a dose of 1.0 μg/kg. However, the study treatment was to be terminated in the case where the platelet count remained above 200,000/μL after 3 weeks or longer discontinuation.

Table 13. Dose adjustment rules (partially modified from the submitted data)

1) Until [redacted], 20[redacted]

Platelet count (/μL)	Dose adjustment
≤10,000	Increase dose by 2 μg/kg (increase weekly).
>10,000 and ≤50,000	Increase dose by 2 μg/kg after 2 consecutive platelet counts fall within this range (increase biweekly).
>50,000 and ≤200,000	May increase or decrease dose by 1 μg/kg at the investigator's discretion and biweekly.
>200,000 and ≤400,000	Decrease dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (decrease biweekly).
>400,000	Hold the scheduled dose on the day, and resume the treatment at the dose decreased by 1 μg/kg on the next or later scheduled treatment day if the platelet count have decreased to ≤200,000/μL.

2) From [redacted], 20[redacted]

Platelet count (/μL)	Dose adjustment
<10,000	Increase dose by 1 μg/kg (increase weekly).
≥10,000 and <50,000	Increase dose by 1 μg/kg after 2 consecutive platelet counts fall within this range (increase biweekly).
≥50,000 and ≤200,000	Continue the same dose. May increase or decrease the dose by 1 μg/kg at the investigator's discretion and should not change the dose weekly (the same dose should be used at least twice).
>200,000 and ≤400,000	Decrease by 1 μg/kg when 2 consecutive platelet counts fall within this range (decrease biweekly).
>400,000	Hold the scheduled dose on the day, and resume the treatment at the dose decreased by 1 μg/kg[a] on the next or later scheduled treatment day if the platelet count has decreased to ≤200,000/μL.

a: If the platelet count increases as a consequence of initiation or increased dose of the other ITP therapy, romiplostim treatment should be resumed at the same dose after the platelet count decreases to ≤200,000/μL.

The main inclusion criteria were as follows: patients who had completed a clinical study of romiplostim in ITP patients in Japan; and the platelet count measured during the screening period was <50,000/μL.

All of the 44 subjects enrolled by the data cutoff time point of [redacted], 20[redacted] received romiplostim. As of the data cutoff time point, the study treatment reached Week 24 in 32 subjects, Week 48 in 19 subjects, Week 96 in 9 subjects, and at least Week 120 in 8 subjects. After the initiation of the romiplostim treatment, a total of 3 subjects was discontinued from the treatment due to the request from the subject (2 subjects) and judgment of the investigator (1 subject), and the study treatment is ongoing in 41 subjects. As of the database snapshot time point of [redacted], 20[redacted], the study drug had been administered for 4 to 132 weeks, and the treatment period (median [first quartile, third quartile]) was 47.9 weeks (24.0, 61.9 weeks) and the number of doses received was 44.5 doses (21.5, 57.5 doses). The cumulative dose was 7540.0 μg (2493.8, 17,940.0 μg) and the mean weekly dose was 3.5 μg/kg (1.8, 5.5 μg/kg). The median dose at Week 1 was 3.0 μg/kg, and then the dose was increased; the median dose remained ≥4.0 μg/kg from Week 15 onward and remained ≥6.0 μg/kg from Week 48 onward, and was 8.0 μg/kg at Week 132.

As for the background of the enrolled subjects, 17 subjects (38.6%) had been splenectomized and 21 subjects (47.7%) had undergone *H. pylori* eradication therapy at the baseline, and 29 subjects (65.9%) and 2 subjects (4.5%) were concomitantly receiving corticosteroids and azathioprine, respectively, as the ITP therapy at the initiation of this study. The baseline platelet count at the time of screening of the previous study was 16,100 ± 9200/μL (mean ± SD) with the median of 16,500/μL (min.-max., 3000/μL-32,000/μL).

For the efficacy, 42 of 44 subjects (95.5%; 95% CI, 84.5%-99.4%) showed a positive platelet response (in this study, defined as the increase in platelet count to ≥ twice the baseline and to ≥50,000/μL [in this study, the baseline platelet count was defined as the baseline count in the previous study]). In 13 of 44 subjects (29.5%), the platelet count increased to ≥400,000/μL. Platelet counts (median) over time in the study were as shown in Figure 9.

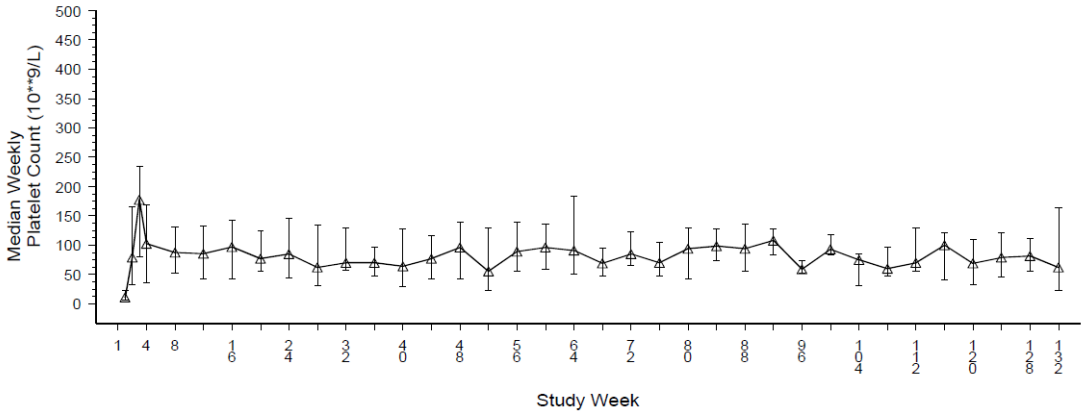


Figure 9. Platelet counts over time (median [first quartile, third quartile])
(partially modified from the submitted data)

The percentage of the subjects with a positive platelet response was 63.6% (28 of 44 subjects) at Week 2 and 84.1% (37 of 44 subjects) at Week 3 and then largely remained in the range of 60% to 80%. At the initiation of this study, 24 of 44 subjects (54.5%) concomitantly received ITP therapies. Of these, 19 subjects received 1 therapy, and 5 subjects received 2 therapies. Concomitant ITP therapies were discontinued in 5 of 24 subjects (20.8%). Of the 44 subjects, 8 subjects (18%) received salvage therapies to increase the platelet count. Prednisolone was most frequently administered (4 subjects) followed by platelet transfusion (3 subjects).

For the safety, the incidence of adverse events was 90.9% (40 of 44 subjects), and adverse events reported by ≥3 subjects were as shown in Table 14.

Table 14. Adverse events reported by ≥3 subjects
(partially modified from the submitted data)

MedDRA ver 12.0 PT	Romiplostim (n = 44)	MedDRA ver 12.0 PT	Romiplostim (n = 44)
Number of subjects with any adverse event	40 (91)	Epistaxis	4 (9)
Nasopharyngitis	25 (57)	Rash	4 (9)
Headache	15 (34)	Wound	4 (9)
Back pain	9 (20)	Constipation	3 (7)
Contusion	8 (18)	Depression	3 (7)
Malaise	7 (16)	Eczema	3 (7)
Pain in extremity	5 (11)	Excoriation	3 (7)
Vertigo	5 (11)	Musculoskeletal stiffness	3 (7)
Abdominal pain upper	4 (9)	Nausea	3 (7)
Arthralgia	4 (9)	Pharyngitis	3 (7)
Diarrhoea	4 (9)	Upper respiratory tract inflammation	3 (7)

n (%)

Neither deaths nor adverse events leading to study discontinuation were reported. Other serious adverse events were reported by 6 of 44 subjects (13.6%). These events included haemorrhagic anaemia, thrombocytopenia, appendicitis, grand mal convulsion, transient ischaemic attack, epistaxis, aneurysm in 1 subject each, but a causal relationship to the study drug was ruled out for all the events. As a serious adverse event related to thrombosis/thromboembolism, transient ischaemic attack occurred in 1 subject (2.3%), but its causal relationship to the study drug was ruled out. Throughout the study period, laboratory value changes were observed in some subjects, but no clinical significance was observed in any of the changes except for the platelet count.

Regarding the number of subjects with antibodies binding to romiplostim, results of the antibody test from 38 subjects are available as of [redacted], 20[redacted]. Of these, 2 subjects (5.3%) were tested positive for antibodies binding to romiplostim or TMP of romiplostim and 1 subject (2.6%) was tested positive for antibodies binding to TPO at the baseline. After the initiation of the study treatment, 3 subjects (7.9%) negative for antibodies binding to romiplostim at the baseline became positive. One of the 3 subjects remained positive until the last sampling. After the initiation of the study treatment, 2 subjects (5.3%) negative for antibodies binding to TPO at the baseline became positive. One of the 2 subjects remained positive until the last sampling. All of the subjects were tested negative for antibodies neutralizing romiplostim and TPO. Furthermore, in any subject, the platelet response was not affected, and neither severe nor serious adverse events occurred.

4.(iii).A.(4).2) Foreign long-term extension study (Foreign study 20030213, Attached document 5.3.5.2-1, Studied period [redacted] 20[redacted] to [redacted] 20[redacted] [database snapshot, [redacted], 20[redacted]])

An open-label, long-term extension study was conducted at 108 centers in the U.S., Canada, the EU, or Australia to evaluate the safety and efficacy of long-term extension treatment with romiplostim. In this study, romiplostim was administered once weekly to ITP patients who had completed Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20040209, 20060131, or 20060195.

To the subjects who received romiplostim in the previous study, administration of romiplostim was started at the final dose in the previous study. For the subjects who received placebo in the previous study, administration of romiplostim was started at the dose of 1 μg/kg. The dose was subcutaneously given once weekly, and the dose was adjusted to maintain the platelet count >50,000/μL according to the dose adjustment rules based on the platelet count. The dose adjustment rules were revised 3 times ([redacted], 20[redacted], [redacted], 20[redacted], [redacted], 20[redacted]), and the final version was set as shown in Table 15. The highest dose was initially set at 30 μg/kg, but changed to 15 μg/kg ([redacted], 20[redacted]) and further re-changed to 10 μg/kg ([redacted], 20[redacted]). When the highest dose was changed to romiplostim 10 μg/kg, the subjects already receiving the dose of >10 μg/kg continued to receive the same dose, but the dose-increase was prohibited. However, once the dose was decreased to ≤10 μg/kg in these subjects, the re-increase of dose to >10 μg/kg was prohibited. The subjects were to discontinue the study if 4 consecutive platelet counts remained <20,000/μL even at the dose of ≥10 μg/kg. When the dose had to be decreased during the study treatment with romiplostim 1.0 μg/kg, treatment was to be discontinued until the platelet count decreased to ≤50,000/μL, and then administration was to be resumed at the dose of 1.0 μg/kg. For subjects aged <18 years, the dose was adjusted every 12 weeks based on body weight.

Table 15. Dose adjustment rules (partially modified from the submitted data)

Protocol version 3 ([redacted] 20[redacted])

Platelet count (/μL)	Dose adjustment[b]
<50,000	Increase dose by 1 μg/kg (increase weekly).
≥50,000 and ≤400,000	Increase or decrease dose by 1 μg/kg to maintain the platelet count at 50,000/μL to 200,000/μL (adjust biweekly).
>400,000[a]	Hold the scheduled dose on the day, and resume the treatment at the dose decreased by 1 μg/kg when the platelet count decreases to below 200,000/μL.

a: If the platelet count increases as a consequence of the initiation or increased dose of the other ITP therapy, the romiplostim treatment should be resumed at the same dose after the platelet count decreases to below 200,000/μL.

b: For the subjects who weighed ≤125 kg, the dose was adjusted by 1 μg/kg, but for subjects who weighed >125 kg, the dose was to be adjusted by smaller increments or decrements (0.25, 0.5, 0.75 μg/kg).

The main inclusion criterion was patient who had completed a study of romiplostim.

A total of 313 ITP patients including 292 adults and 21 children were enrolled. Of these, 310 patients including 291 adults and 19 children received romiplostim. As 69 adults and 2 children discontinued the study treatment by the database snapshot time point in [redacted] 20[redacted], the treatment is ongoing in a total of 239 patients including 222 adults and 17 children. In adults, the most frequent reason for study discontinuation was consent withdrawal (21 subjects) followed by the occurrence of adverse events, another therapy, and deaths (10 subjects each). The median treatment period was 48 weeks, and in 4 patients having received the treatment for 240 to 252 weeks by that time, it is still ongoing. The dose of romiplostim at the initiation of the treatment in 291 adult subjects was 3.5 ± 3.2 μg/kg (mean ± SD). After the initiation, the mean dose was changed to ≥4.0 μg/kg at Week 4 and then ≥5.0 μg/kg at Week 12 and thereafter, and remained approximately 6.0 μg/kg at Week 44 and thereafter.

Of 292 adult subjects, 95 subjects (32.5%) had been splenectomized, and 37 subjects (12.7%) had been concomitantly receiving the ITP therapy. At the initiation of this study, the baseline platelet count was 72,600 ± 84,700/μL (mean ± SD).

For the efficacy in adult subjects, 273 of 291 subjects (93.8%; 95% CI, 90.4%-96.3%) showed a positive platelet response (in this study, defined as the platelet count being increased to ≥50,000/μL). The platelet count increased to ≥100,000/μL in 258 of 291 subjects (88.7%), ≥150,000/μL in 239 of 291 subjects (82.1%), and ≥400,000/μL in 105 of 291 subjects (36.1%). The median platelet count at the initiation of the treatment was 35,000/μL, and the platelet count was ≥50,000/μL in 106 of 289 subjects (36.7%). The platelet counts (median) over time in the study were as shown in Figure 10.

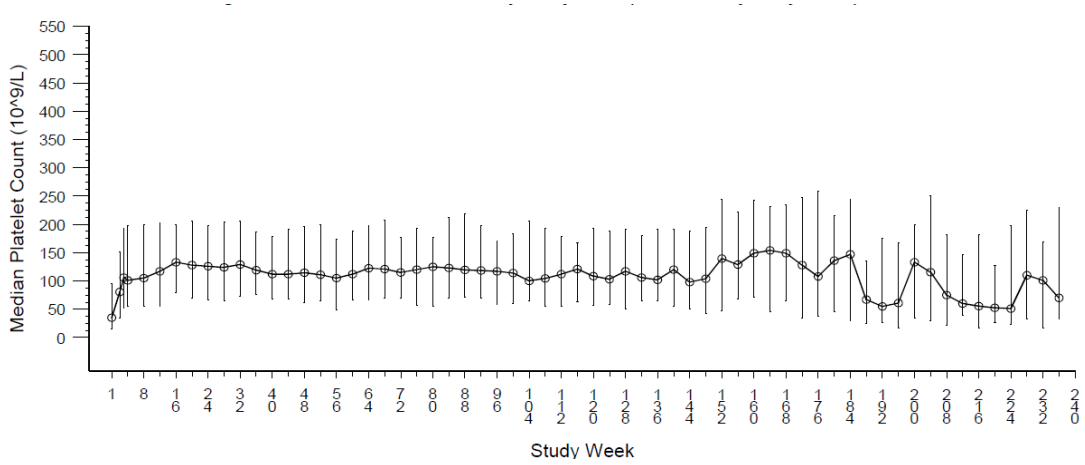


Figure 10. Platelet counts over time (median [first quartile, third quartile]) (partially modified from the submitted data)

The percentage of the subjects with a positive platelet response was increased to 62.5% (175 of 280 subjects) at Week 2 and to 72.7% (205 of 282 subjects) at Week 3 and thereafter generally remained in the range of 60% to 70%.

Of the 291 adult subjects, 37 subjects were concomitantly receiving the ITP therapy at the initiation of this study. After the initiation, 18 of the 37 subjects (48.6%) discontinued the concomitant ITP therapy, and 84 of 291 subjects (28.9%) received the salvage therapy to increase the platelet count. Immunoglobulin was most frequently administered as the salvage therapy (36

subjects) followed by prednisone (31 subjects), platelet transfusion (17 subjects), dexamethasone (16 subjects), and methylprednisolone succinate (12 subjects).

For the safety in adult subjects, adverse events were reported by 267 of 291 subjects (91.8%), and the adverse events with incidence of ≥10% were as shown in Table 16.

Table 16. Adverse events with incidence of ≥10% (adult)
(partially modified from the submitted data)

MedDRA ver 12.0 PT	Adults (n = 291)
Number of subjects with any adverse event	267 (91.8)
Headache	92 (31.6)
Nasopharyngitis	86 (29.6)
Contusion	81 (27.8)
Fatigue	81 (27.8)
Epistaxis	69 (23.7)
Arthralgia	66 (22.7)
Diarrhoea	66 (22.7)
Upper respiratory tract inflammation	66 (22.7)
Nausea	60 (20.6)
Cough	59 (20.3)
Petechiae	47 (16.2)
Dizziness	44 (15.1)
Back pain	43 (14.8)
Pain in extremity	43 (14.8)
Gingival bleeding	39 (13.4)
Rash	39 (13.4)
Vomiting	39 (13.4)
Oropharyngeal pain	37 (12.7)
Insomnia	35 (12.0)
Oedema peripheral	35 (12.0)
Haematoma	34 (11.7)
Sinusitis	34 (11.7)
Pyrexia	33 (11.3)
Urinary tract infection	31 (10.7)

n (%)

Adverse events resulting in deaths were reported by 13 of 291 subjects (4.5%). They included myocardial infarction in 3 subjects, and thrombocytopenia, angina unstable, cardiac arrest, cardiac failure congestive, meningitis, pneumococcal sepsis, pneumonia, progressive multifocal leukoencephalopathy, hepatic neoplasm malignant, and renal failure in 1 subject each. The causal relationships to the study drug could not be ruled out for angina unstable or cardiac arrest.

Serious adverse events were reported by 96 of 291 subjects (33.0%), and serious adverse events reported by ≥2 subjects were as shown in Table 17.

Table 17. Serious adverse events reported by ≥2 subjects (adult)
(partially modified from the submitted data)

MedDRA ver 12.0 PT	Adults (n = 291)
Number of subjects with any adverse event	96 (33.0)
Thrombocytopenia	19 (6.5)
Pneumonia	6 (2.1)
Bone marrow disorder	5 (1.7)
Myocardial infarction	5 (1.7)
Idiopathic thrombocytopenic purpura	4 (1.4)
Cardiac failure congestive	4 (1.4)
Pyrexia	4 (1.4)
Dehydration	4 (1.4)
Dyspnoea	4 (1.4)
Cardiac failure	3 (1.0)
Chest pain	3 (1.0)
Osteoarthritis	3 (1.0)
Renal failure	3 (1.0)
Epistaxis	3 (1.0)
Acute myocardial infarction	2 (0.7)
Angina unstable	2 (0.7)
Atrial fibrillation	2 (0.7)
Coronary artery disease	2 (0.7)
Vertigo	2 (0.7)
Gastrointestinal haemorrhage	2 (0.7)
Gingival bleeding	2 (0.7)
Rectal haemorrhage	2 (0.7)
Hernia obstructive	2 (0.7)
Oedema peripheral	2 (0.7)
Appendicitis	2 (0.7)
Bronchitis	2 (0.7)
Catheter related infection	2 (0.7)
Cellulitis	2 (0.7)
Urosepsis	2 (0.7)
Hip fracture	2 (0.7)
Platelet count increased	2 (0.7)
Hyperkalaemia	2 (0.7)
Hepatic neoplasm malignant	2 (0.7)
Convulsion	2 (0.7)
Syncope	2 (0.7)
Transient ischaemic attack	2 (0.7)
Mental status changes	2 (0.7)
Renal failure acute	2 (0.7)
Vaginal haemorrhage	2 (0.7)
Petechiae	2 (0.7)
Knee arthroplasty	2 (0.7)
Deep vein thrombosis	2 (0.7)
Thrombosis	2 (0.7)

n (%)

Adverse events leading to study discontinuation were reported by 20 of 291 subjects (6.9%). They included myocardial infarction in 3 subjects, bone marrow disorder in 2 subjects, and bicytopenia, angina unstable, cardiac arrest, cardiac failure congestive, hepatic failure, pneumococcal sepsis, pneumonia, thrombophlebitis septic, platelet count decreased, hepatic neoplasm malignant, lymphoma, multiple myeloma, myelofibrosis, renal failure, vaginal haemorrhage, dermatitis exfoliative, systemic lupus erythematosus rash, and deep vein thrombosis in 1 subject each. A causal relationship to the study drug could not be ruled out for any of the events.

Thrombosis/thromboembolism-related adverse events were reported by 17 of 291 subjects (5.8%). They included myocardial infarction (5 subjects), acute myocardial infarction (3), deep vein thrombosis, thrombosis, and transient ischaemic attack (2 each), and blindness transient, catheter thrombosis, cerebrovascular accident, coronary arterial stent insertion, coronary artery occlusion, paresis, portal vein thrombosis, pulmonary embolism, thrombophlebitis, transverse sinus thrombosis (1 each). Of these, 3 subjects (1.0%) who experienced acute myocardial infarction died.

Throughout the study period, laboratory value changes were observed in some subjects, but no clinical significance was observed in any of the changes except for the platelet count.

Of 291 subjects, 18 subjects (6.2%) and 16 subjects (5.5%) were tested positive for antibodies binding to romiplostim and TPO, respectively, before the initiation of the treatment. After the initiation, 12 subjects (4.1%) became positive for antibodies binding to romiplostim, and of these, 2 subjects were further positive for neutralizing antibodies. Follow-up on these 2 subjects revealed that both became negative for neutralizing antibodies. After the initiation of the treatment, 5 subjects (1.7%) became positive for antibodies binding to TPO. Of these, 2 subjects were transiently positive and returned to be negative at the final test during the treatment period, but 3 subjects remained positive even at the final test. All of these positive subjects were negative for antibodies neutralizing TPO and thus showed a positive platelet response. Some subjects, other than the subjects positive for antibodies neutralizing romiplostim, became positive for antibodies binding to TPO.

4.(iii).A.(5) Other studies

4.(iii).A.(5).1) Foreign phase III supplemental study (Foreign study 20050123, Attached document 5.3.5.4-2, Studied period August 2005 to October 2006)

An open-label study was conducted at 6 centers in the U.S. to investigate the effects of long-term treatment with romiplostim on bone-marrow morphology, especially the effects of increased megakaryocytes on increase of reticulin, in adult patients with thrombocytopenia associated with ITP (splenectomized and non-splenectomized patients). In this study, adult ITP patients who were transferred from Study 20030105 or 20030212 to Study 20030213, a long-term extension study, were included (target sample size, 20 subjects). In the study, romiplostim was not administered.

The main inclusion criterion was adult ITP patient who underwent biopsy of bone marrow within 1 year before participation in Study 20030105 or 20030212.

The study enrolled a total of 10 patients, including 7 splenectomized patients who participated in Study 20030105 and 3 non-splenectomized patients who participated in Study 20030212. Of these 10 patients, 4 patients, assigned first to placebo and then to romiplostim groups, received romiplostim for 3 months; 5 patients, assigned first to romiplostim and then to romiplostim groups, received romiplostim for 9 months; and 1 patient, assigned to first romiplostim and then romiplostim groups, received romiplostim for 6 months in their previous studies.

Detailed changes in the bone marrow before and after the romiplostim treatment, the primary endpoint, were as shown in Table 18. The baseline in this table indicates the baseline in Study 20030105 or 20030212, while the follow-up time point indicates the time point after 3, 6, or 9 months of treatment.

Table 18. Bone marrow examination (partially modified from the submitted data)

	Baseline (n = 10)	Follow-up (n = 10)
M/E ratio		
Number of subjects	7	6
Mean	2.86	2.78
SD	1.36	0.61
Median	2.60	2.80
Q1, Q3	1.70, 3.30	2.30, 3.10
Minimum, maximum	1.7, 5.6	2.0, 3.7
Cellularity, %		
Number of subjects	10	9
Mean	47.5	57.2
SD	12.3	19.4
Median	50.0	50.0
Q1, Q3	40.0, 60.0	50.0, 60.0
Minimum, maximum	25, 60	25, 95
Megakaryocyte count (/1 visual field)		
Number of subjects	10	9
Mean	5.05	7.81
SD	3.07	6.33
Median	4.55	6.50
Q1, Q3	2.70, 6.90	2.70, 10.60
Minimum, maximum	1.7, 12.0	0.1, 21.1
Reticulin, number of subjects (%)		
Negative	7 (70.0)	6 (60.0)
Mild	1 (10.0)	2 (20.0)
Moderate	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Not performed	2 (20.0)	2 (20.0)
Iron development, number of subjects (%)		
0	1 (10.0)	2 (20.0)
+1	2 (20.0)	3 (30.0)
+2	0 (0.0)	0 (0.0)
+3	0 (0.0)	0 (0.0)
+4	0 (0.0)	0 (0.0)
Not performed	7 (70.0)	5 (50.0)
Ringed sideroblast count, number of subjects (%)		
None	3 (30.0)	6 (60.0)
Present, <15%	0 (0.0)	0 (0.0)
Present, >15%	0 (0.0)	0 (0.0)
Not performed	7 (70.0)	4 (40.0)
Trichrome staining, number of subjects (%)		
Negative	8 (80.0)	8 (80.0)
Mild	0 (0.0)	0 (0.0)
Moderate	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Not performed	2 (20.0)	2 (20.0)

Reticulin of 6 subjects was measured at both baseline and follow-up time point after 3, 6, or 9 months of the romiplostim treatment. Of them, only 1 subject showed the change of the reticulin status from “negative” to “mild,” and its clinical significance was unknown.

As the secondary endpoints, the dose range of romiplostim, treatment period, or effect of splenectomy on the bone marrow morphology was investigated. In 10 subjects enrolled in the study, the number of doses received (median [range]) was 25.0 doses (10-37 doses); cumulative dose, 4905.0 μg (1325-13,050 μg); and mean weekly dose, 3.1 μg/kg (2-6 μg/kg) and 180.3 μg

(112-393 μg). The subject who experienced an adverse event of B-cell lymphoma in the phase III study (Study 20030212) discontinued the study.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning

PMDA asked the applicant to explain the positioning of romiplostim and the anticipated therapy choice between conventional supportive measures and romiplostim in treating ITP.

The applicant explained as follows:
In Japan, the standard treatment for ITP differs depending on the patient background: *H.pylori* eradication is preferentially indicated for *H.pylori*-positive patients; corticosteroid therapy is indicated for *H.pylori*-positive patients who have not responded to the eradication as well as *H.pylori*-negative patients; and splenectomy may be considered as the primary surgical treatment for patients in whom the corticosteroid therapy has not been sufficiently effective, cannot be continued or is contraindicated (*Research for overcoming intractable diseases funded by Health and Labour Sciences Research Grants, FY 2004 Summary report of unit research on Investigation research on coagulopathy* 2005;13-26). For patients in whom the corticosteroid therapy has not been sufficiently effective and also splenectomy is contraindicated, or who do not provide their consent to splenectomy, the secondary treatment includes immunosuppressants such as danazol and azathioprine, although their evidence level is low. In addition, immunoglobulin preparations and platelet transfusion are used when emergent blood coagulation is required. In Europe and the U.S., in addition to the emergency use, immunoglobulin preparations are used for patients in whom corticosteroids have not been sufficiently effective or are inappropriate. Prior to use of romiplostim, treatment with immunoglobulin preparations is considered. Romiplostim is a drug that enhances the platelet production unlike the existing drugs, which suppress the destruction of platelets through immunosuppression, and the submitted clinical study data have demonstrated the efficacy and safety of romiplostim regardless of splenectomy status. Romiplostim is planned to be indicated for adult chronic ITP patients in whom corticosteroid therapy cannot be continued due to the adverse drug reactions, it is contraindicated, or it has not been sufficiently effective. Romiplostim may also be administered to patients in whom splenectomy is determined to be inappropriate, who wish for internal treatment, or in whom splenectomy has not been sufficiently effective, and it may be chosen more than the current secondary treatment with immunosuppressants. In addition, in the phase III studies (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212), patients concomitantly receiving corticosteroid, azathioprine or danazol at a fixed dose were included, and analysis between sub-groups with and without such concomitant therapy also suggested the efficacy of romiplostim. Accordingly, romiplostim can be used concomitantly for patients who have not sufficiently responded to these therapeutic drugs, have to discontinue these drugs or have to have the dose reduction due to adverse drug reactions.

PMDA considers as follows:
Regarding clinical positioning of romiplostim, the applicant claims that romiplostim can be indicated for chronic ITP patients who have not sufficiently responded to the standard treatment such as corticosteroids. Taking into account that Japanese study 20[redacted]0216 demonstrated the efficacy and safety of romiplostim in patients who had previously received at least 1 type of ITP therapy and had the platelet count <30,000/μL at the baseline, the applicant's claim is appropriate. Romiplostim can be thus positioned as one option in the case where further ITP therapy is indicated after the standard treatment. In addition, the efficacy and safety have been demonstrated in splenectomized patients in Foreign study 20030105 as well as in non-splenectomized patients in Foreign study 20030212. This result suggests romiplostim can be a treatment option comparable to splenectomy. On the other hand, there is not enough evidence to convince that preference be given more to romiplostim than to the other ITP therapies, because study data directly comparing romiplostim and the other ITP therapies are not available and the efficacy and safety of long-term treatment with romiplostim have not been clearly demonstrated. Accordingly,

appropriateness of romiplostim therapy has to be carefully judged by physicians with adequate knowledge and experience in ITP therapy after thorough consideration of the efficacy and safety of the other treatment options.

There is poor evidence with the use of romiplostim prior to corticosteroids and the use of romiplostim is not recommended actively in patients who have difficulty with corticosteroids. However, in consideration of the seriousness of the target disease, romiplostim may be used when the benefit can outweigh the risk.

PMDA has confirmed that romiplostim is listed as an option of the secondary therapeutic drugs for ITP in the updated international consensus report (Provan D et al. *Blood*. 2010;115:168-86).

4.(iii).B.(2) Use of foreign clinical study data

PMDA asked the applicant to explain the appropriateness of use of the foreign study data for demonstrating the efficacy and safety of romiplostim in Japanese ITP patients.

The applicant responded as follows:

Although the number of subjects was limited (4 Japanese subjects, 11 foreign subjects), the Japanese and foreign long-term extension studies in adult ITP patients showed comparable pharmacokinetic profiles. The pharmacodynamics is comparable between Japanese and foreign patients based on the following reasons: (1) no marked differences were found in platelet counts or baseline-normalized platelet counts between the Japanese and foreign phase II studies; (2) the platelet counts over time and dose over time at Week 10 and thereafter were almost comparable between the Japanese and foreign phase III studies; and (3) Japanese and foreign healthy adult subjects showed similar pharmacodynamic dose-response. In addition, the ITP diagnosis criteria in Japan and foreign countries are considered comparable, because under both criteria, diagnosis is made after the haemorrhage findings and platelet count decreased are confirmed, and a possibility of the other diseases potentially causing platelet count decreased is excluded. Furthermore, no marked differences were found in subject background characteristics such as age, sex, and baseline platelet counts between the Japanese and foreign phase III studies (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212). Although the body weight was higher in foreign studies than in Japanese studies, the dose of romiplostim is planned to be determined based on the body weight and it does not cause any problem. Regarding the treatment history, although most of the subjects used corticosteroids, foreign subjects more frequently received immunoglobulin preparations, danazol, and rituximab than Japanese subjects. However, the treatment history has not affected the efficacy of romiplostim [see 4.(iii).B.(3) Efficacy], and thus Japanese and foreign data can be compared. Although the Japanese and foreign phase III studies mostly shared the design, the starting dose (Japanese study, 3 μg/kg; Foreign study, 1 μg/kg) and treatment duration (Japanese study 12 weeks, Foreign study 24 weeks) were different. The efficacy of romiplostim was evaluated by comparing with the placebo in the Phase 3 Efficacy Set including all of the subjects randomized in Japanese and foreign phase III studies (159 subjects [105 subjects in the romiplostim group (22 Japanese subjects, 83 foreign subjects), 54 subjects in the placebo group (12 Japanese subjects, 42 foreign subjects)]). As a result, the numbers of weeks in which the platelet response (the platelet count being increased to ≥50,000/μL) (mean ± SD) was observed between Week 2 and Week 13, the primary endpoint, in romiplostim and placebo groups in the Japanese studies were 9.5 ± 3.3 and 0.2 ± 0.4 weeks, respectively, and in the foreign studies were 6.8 ± 3.9 and 0.5 ± 1.4 weeks, respectively; both Japanese and foreign studies demonstrated the efficacy of romiplostim. However, the time to the target platelet counts in the romiplostim group and platelet counts over time for the first several weeks of the romiplostim treatment were different between Japanese and foreign studies, suggesting that the difference of the starting dose have affected the efficacy. In both Japanese and foreign studies, the platelet count was maintained by the dose adjustment once the target count was reached. As described above, the platelet counts over time during the initial treatment period

might be affected by the difference of the starting dose. However, in both Japanese and foreign studies, the dose was to be adjusted appropriately so that the target platelet count was maintained once it reached the target level (50,000-200,000/μL). Based on that, efficacy evaluation with foreign study data as reference is considered possible. Concerning the safety of romiplostim, the incidence of adverse events was compared between the Japanese and foreign subjects in the Phase 3 ITP Safety Set including all of the subjects who received the study drug at least once in Japanese or foreign phase III studies in ITP patients (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212) (159 subjects [106 subjects in the romiplostim group (22 Japanese subjects, 84 foreign subjects), 53 subjects in the placebo group (12 Japanese subjects, 41 foreign subjects)]). As a result, although the incidences of adverse events per 100 patient-years in the romiplostim and placebo groups were slightly different between Japanese and foreign studies, no clinically relevant events were observed; and no significant differences were observed in the incidence of adverse events for the first 3 weeks in which the platelet counts over time differed between the Japanese and foreign studies.

Based on the above investigations of differences in intrinsic and extrinsic ethnic factors between Japanese and foreign subjects as well as comparison of primary efficacy and safety data, it is appropriate to use the foreign study data in discussion of the efficacy and safety of romiplostim in Japanese subjects.

PMDA considers as follows:
It is possible to use the data from Foreign studies 20030105 and 20030212 as references in addition to the data from Japanese study 20[redacted]0216, which included a limited number of patients, in discussion of the efficacy and safety of romiplostim in Japanese subjects, considering that there might be no relevant differences affecting the efficacy and safety evaluation of romiplostim in extrinsic and intrinsic ethnic factors between Japanese and foreign subjects; and in the Japanese and foreign phase III studies, the dosage and administration of romiplostim were adjusted by monitoring the platelet count as appropriate, and no large inconsistencies were observed in the efficacy and safety data between Japanese and foreign subjects except for the different platelet counts over time during the initial treatment period, which was caused by the different starting doses in Japanese and foreign studies.

4.(iii).B.(3) Efficacy

4.(iii).B.(3).1) Appropriateness of the primary endpoint

The applicant explained the appropriateness of the primary endpoint in the Japanese and foreign clinical studies as follows:
In the foreign phase III studies (Studies 20030105 and 20030212), the primary endpoint was set as the percentage of the subjects in whom the platelet count reached ≥50,000/μL in at least 6 measurement sessions during the last 8 weeks of the 24-week treatment period (a total of 8 corresponding measurement sessions from Week 18 to Week 25) (durable platelet response). When the target platelet count (≥50,000/μL) is reached in ITP patients, since the haemorrhage risk has been decreased, ITP therapy is not required in general (George JN et al. *Blood.* 1996;88:3-40, Provan D et al. *Blood.* 2010;115:168-86). Compared with the platelet count (<30,000/μL) set in the inclusion criteria, the target value is considered to have clinical significance. From a viewpoint of verification of continued efficacy, the duration of the durable platelet response is appropriate. On the other hand, in the Japanese study 20[redacted]0216, the primary endpoint was set as the number of weeks in which the platelet response was observed (the platelet count increased to ≥50,000/μL, as weekly measured on the specified day between Week 2 and Week 13), which was different from that in the foreign studies, in consideration of the feasibility. The results of the preceding foreign phase III studies demonstrated that the platelet count increased to ≥50,000/μL in at least 50% of the subjects at Week 4 in splenectomized patients and at Week 3 in non-splenectomized patients. In the Japanese study 20[redacted]0216, the platelet count was expected to exceed 50,000/μL earlier than in the foreign phase III studies because the starting dose in the

Japanese study was 3 μg/kg. Thus, it was predicted that the efficacy of romiplostim could be verified in 12 weeks in Japan, which was shorter than the study period in the foreign studies. As described above, the primary endpoint adopted in the Japanese study was appropriate. The endpoints related to the platelet response were investigated in both Japanese and foreign phase III studies, and the platelet response can be thus compared between Japanese and foreign subjects.

PMDA considers as follows:
According to the "Guideline of ITP therapy for adult patients (JGL)" published in 2004 by the study group of the Ministry of Health, Labour and Welfare, and "A Practice Guideline Developed by Explicit Methods for The American Society of Haematology (ASHGL)" published in 1996 by the American Society of Hematology (ASH), both available at the time of study planning, it was recommend that patients with chronic ITP receive the therapy with the target platelet count ≥50,000/μL. Thus, the primary endpoint was considered to be set rationally to some extent in the Japanese study 20[redacted]0216 and Foreign studies 20030105 and 20030212 and the efficacy of romiplostim can be evaluated based on the data on the primary endpoint. Furthermore, the efficacy of romiplostim should be evaluated based on the data not only on the primary endpoint but also on the secondary endpoints such as the percentage of the subjects with the platelet count increased by a certain level or higher from the baseline, change of the platelet count from the baseline, and percentage of the subjects who received the salvage therapy. In addition, the suppressive effect against development of haemorrhage symptom associated with the increased platelet count is important, and this matter will be discussed in the following section. Romiplostim is not a radical therapeutic drug for ITP and thus is expected to be administered for an extended period, and the information on the safety of long-term use of romiplostim, platelet counts over time, and combination with the other therapies should be appropriately collected after the market launch.

4.(iii).B.(3).2) Efficacy of romiplostim

PMDA considered that the following points in the Japanese study 20[redacted]0216 and Foreign studies 20030105 and 20030212 were important in reviewing the efficacy of romiplostim: (a) the platelet count increasing effects including results on the primary endpoint in each study; (b) the suppressive effect against development of haemorrhage symptom; (c) the efficacy of the long-term use in the open-label long-term extension studies; and (d) the effects of different patient background factors on the efficacy of romiplostim. The points (a) to (d) were reviewed in the following.

4.(iii).B.(3).2).(a) Platelet count increasing effect

The applicant explained the data on the platelet count increasing effects, which was set as the primary endpoint, as follows:
The median number of weeks in which the platelet response was observed, specified as the primary endpoint in the Japanese study 20[redacted]0216 (in this study, defined as the platelet count being increased to ≥50,000/μL, measured on the scheduled day of each week between Weeks 2 and 13) was 0 weeks in the placebo group and 11.0 weeks in the romiplostim group; it was significantly higher in the romiplostim group than in the placebo group. Of the major secondary endpoints, the percentage of the subjects with the platelet count increased by ≥20,000/μL from the baseline was 25.0% (3 of 12 subjects) in the placebo group and 95.5% (21 of 22 subjects) in the romiplostim group; the change from the baseline platelet count to the mean platelet count for the last 4 weeks of the treatment period (mean ± SD) was 2300 ± 6500/μL in the placebo group and 109,700 ± 88,500/μL in the romiplostim group; the number of weeks in which the platelet count increased to ≥50,000/μL and ≤200,000/μL between Week 2 and Week 13 was 0.2 ± 0.4 weeks in the placebo group and 6.3 ± 3.2 weeks in the romiplostim group; and the percentage of the subjects who received the salvage therapy was 16.7% (2 of 12 subjects) in the placebo group and 9.1% (2 of 22 subjects) in the romiplostim group. In consideration of the above, the platelet-increasing effect of romiplostim in Japanese ITP patients has been demonstrated until Week 13,

although the number of the subjects included in the study was limited. The percentage of the subjects with the durable platelet response, set as the primary endpoint in foreign phase III studies (the platelet count was ≥50,000/μL in at least 6 measurement sessions during the last 8 weeks of the 24-week treatment period [a total of 8 measurement sessions from Week 18 to Week 25]), was 0% (0 of 21 subjects) in the placebo group and 38.1% (16 of 42 subjects) in the romiplostim group in the Foreign study 20030105 and 4.8% (1 of 21 subjects) in the placebo group and 61.0% (25 of 41 subjects) in the romiplostim group in the Foreign study 20030212; in both studies, the percentage in the romiplostim group was significantly higher than that in the placebo group. Based on the above data, the platelet-increasing effect of romiplostim was demonstrated.

PMDA accepted the above explanation and determined that romiplostim has the platelet-increasing effect by which the platelet count will increase to a level realizing a decreased haemorrhage risk in ITP patients.

4.(iii).B.(3).2).(b) Suppressive effect against development of haemorrhage symptom

The applicant explained the relationship between haemorrhage events and platelet count in clinical studies as follows:

Haemorrhage-related adverse events by platelet count at the time of their onset were investigated in the Phase 3 ITP Long-Term Safety Set (205 subjects; 46 Japanese subjects, 159 foreign subjects) consisting of the subjects in the Japanese and foreign phase III studies (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212) and long-term extension studies (Japanese study 20[redacted]0113, Foreign study 20030213) (Table 19). Adverse events of epistaxis, petechiae, gingival bleeding, and ecchymosis are frequently observed in association with ITP. The incidence of any of the events is higher in the patients with the platelet count <50,000/μL. In addition, clinical study data also suggested that development of haemorrhagic events could be suppressed by maintaining the platelet count ≥50,000/μL.

Table 19. Haemorrhage-related adverse events of ≥5 cases in either patient subgroup (by platelet count at the time of onset) (Phase 3 ITP Long-Term Safety Set) (partially modified from the submitted data)

	Non-romiplostim-treated subgroup				Romiplostim-treated subgroup			
Platelet count at the time of onset (/μL)	<50,000	50,000 to <200,000	200,000 to <400,000	≥400,000	<50,000	50,000 to <200,000	200,000 to <400,000	≥400,000
Number of weeks	996	110	29	11	3673	9581	2302	531
Epistaxis	15 (1.5)	1 (0.9)	0 (0)	0 (0)	75 (2.0)	57 (0.6)	11 (0.5)	4 (0.8)
Petechiae	15 (1.5)	0 (0)	0 (0)	0 (0)	46 (1.3)	15 (0.2)	6 (0.3)	3 (0.6)
Ecchymosis	9 (0.9)	1 (0.9)	0 (0)	0 (0)	15 (0.4)	10 (0.1)	0 (0)	0 (0)
Gingival bleeding	8 (0.8)	0 (0)	0 (0)	0 (0)	19 (0.5)	6 (0.1)	2 (0.1)	1 (0.2)
Injection site haematoma	6 (0.6)	0 (0)	0 (0)	0 (0)	9 (0.2)	14 (0.1)	2 (0.1)	0 (0)
Purpura	3 (0.3)	0 (0)	0 (0)	0 (0)	4 (0.1)	1 (0)	1 (0)	1 (0.2)
Mouth haemorrhage	3 (0.3)	0 (0)	0 (0)	0 (0)	13 (0.4)	8 (0.1)	1 (0)	0 (0)
Vaginal haemorrhage	2 (0.2)	0 (0)	0 (0)	0 (0)	9 (0.2)	2 (0)	1 (0)	0 (0)
Gastrointestinal haemorrhage	2 (0.2)	0 (0)	0 (0)	0 (0)	6 (0.2)	1 (0)	0 (0)	0 (0)
Haematoma	1 (0.1)	0 (0)	0 (0)	0 (0)	12 (0.3)	10 (0.1)	1 (0.0)	0 (0)
Conjunctival haemorrhage	1 (0.1)	0 (0)	0 (0)	0 (0)	2 (0.1)	7 (0.1)	1 (0.0)	1 (0.2)
Erythema	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.1)	1 (0.0)	0 (0)
Rectal haemorrhage	1 (0.1)	0 (0)	0 (0)	0 (0)	4 (0.1)	4 (0.0)	1 (0.0)	0 (0)
ITP	0 (0)	0 (0)	0 (0)	0 (0)	17 (0.5)	4 (0.0)	2 (0.1)	1 (0.2)
Menorrhagia	0 (0)	0 (0)	0 (0)	0 (0)	5 (0.1)	3 (0.0)	1 (0.0)	0 (0)
Ocular hyperaemia	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.1)	2 (0.0)	0 (0)	0 (0)
Haemoptysis	0 (0)	0 (0)	0 (0)	0 (0)	4 (0.1)	0 (0)	0 (0)	1 (0.2)
Haematochezia	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.1)	1 (0.0)	1 (0.0)	0 (0)

Number of events (events/100 weeks)

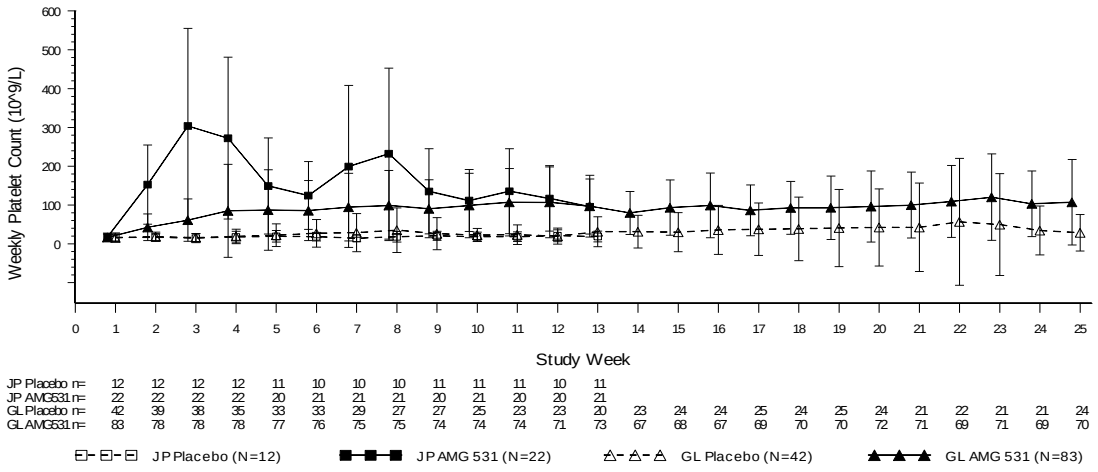
PMDA accepted the above explanation and considered that the increased platelet count by romiplostim can be expected to suppress the development of haemorrhage symptoms in chronic ITP patients.

4.(iii).B.(3).2).(c) Efficacy of long-term treatment with romiplostim

The applicant explained the efficacy of long-term treatment with romiplostim as follows:

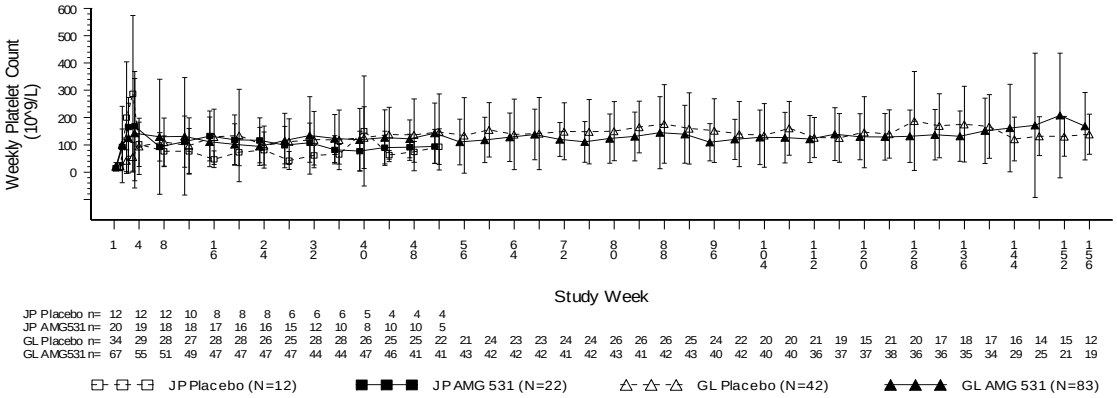
Of the subjects who completed the Japanese and foreign phase III studies (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212), patients who needed to continue romiplostim treatment (the platelet count decreased to <50,000/μL after the completion of the study) were enrolled in the long-term extension studies (Japanese study 20[redacted]0113, Foreign study 20030213). The efficacy of long-term treatment with romiplostim was evaluated in an efficacy set (Phase 3 Long-Term Efficacy Set) consisting of 135 subjects enrolled in the long-term extension studies. The evaluation period started at the baselines of the previous studies, and the data before the long-term extension studies (Japanese study, Weeks 1 to 13; foreign study, Weeks 1 to 25) and after enrollment in the long-term extension studies (Japanese study, Weeks 1 to 52 after enrollment; foreign study, Weeks 1 to 156 after enrollment) are separately presented.

The platelet counts over time in the subjects in the Japanese and foreign studies before the long-term extension studies were as shown in Figure 11. In the Japanese romiplostim group before the long-term extension study, the mean platelet count reached the lower limit of the target platelet count range (50,000/μL) immediately after the initiation of treatment and then generally remained within the target range although it exceeded the upper limit (200,000/μL) in some weeks. On the other hand, in the foreign romiplostim group, the platelet count gradually increased after the initiation of treatment and, at Week 3 and thereafter, remained within the target range (50,000-200,000/μL) without exceeding the upper limit. The platelet counts over time in the subjects in the Japanese and foreign studies after enrollment in the long-term extension studies were as shown in Figure 12. In the Japanese and foreign long-term extension studies, the platelet count in the romiplostim (before long-term treatment) to romiplostim (in long-term treatment) sub-group remained within the target range at Week 2 and thereafter in the long-term treatment. On the other hand, the platelet count in the "placebo (before long-term treatment) to romiplostim (in long-term treatment)" sub-group at Week 2 exceeded the upper limit of the target platelet count range in the Japanese study, but did not exceed the upper limit in the foreign study. In both studies, the platelet count after that remained within the target range. The difference in the platelet counts over time immediately after the initiation of romiplostim treatment between the Japanese and foreign subjects was considered attributable to the different starting doses. Based on the above data, the efficacy of long-term treatment with romiplostim was maintained.



JP: Japanese phase III studies, GL: Foreign phase III studies

Figure 11. Platelet counts over time before long-term extension studies (Phase 3 Long-Term Efficacy Set, mean ± SD) (partially modified from the submitted data)



JP: Japanese long-term extension study, GL: Foreign long-term extension study
Placebo: "Placebo → romiplostim" group, AMG531: "romiplostim → romiplostim" group

Figure 12. Platelet counts over time in long-term extension studies (Phase 3 Long-Term Efficacy Set, mean ± SD) (partially modified from the submitted data)

PMDA considers as follows:
Based on the data from the open-label long-term extension studies (Japanese study 20[redacted]0113, Foreign study 20030213), the efficacy of romiplostim can be maintained even during the long-term treatment. However, the number of the subjects treated with romiplostim for an extended period is currently limited in Japan, and the efficacy and safety of long-term (over several years) treatment with romiplostim are unknown. Therefore, information should be collected from the clinical practice continuously and actively after the market launch and provided to the healthcare providers in clinical settings as needed.

4.(iii).B.(3).2).(d) Effects of patient background factors on the efficacy of romiplostim
The applicant performed the sub-group analysis based on each patient's background factors at the baseline (ITP treatment history, splenectomy status, concomitant ITP therapy status, platelet count, *H.pylori* eradication status).

The applicant explained their effects on the efficacy of romiplostim as follows:

a) ITP treatment history at the baseline
The applicant explained as follows:
Table 20 shows the ITP treatment history of the subjects at the baseline in the Japanese study 20[redacted]0216 and Foreign studies 20030105 and 20030212, and Tables 21 and 22 show the efficacy data in each of sub-groups stratified by number of previous ITP treatments (≤3, >3). The efficacy was not largely different between sub-groups in the romiplostim group in any of the studies, and the efficacy of romiplostim can be expected irrespective of the ITP treatment history at the baseline.

Table 20. ITP treatment history at the baseline
(Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212)
(partially modified from the submitted data)

	Study 20[redacted]0216		Studies 20030105/20030212	
	Placebo group (12 subjects)	Romiplostim group (22 subjects)	Placebo group (42 subjects)	Romiplostim group (83 subjects)
ITP treatment history at the baseline				
Corticosteroids	12 (100.0)	22 (100.0)	39 (92.9)	79 (95.2)
Immunoglobulin preparations	8 (66.7)	11 (50.0)	38 (90.5)	70 (84.3)
Chemotherapy	0 (0.0)	5 (22.7)	12 (28.6)	21 (25.3)
Danazol	2 (16.7)	3 (13.6)	21 (50.0)	27 (32.5)
Azathioprine	4 (33.3)	5 (22.7)	11 (26.2)	19 (22.9)
Rituximab	0 (0.0)	3 (13.6)	20 (47.6)	43 (51.8)
H.pylori eradication	3 (25.0)	11 (50.0)	-	-
Others	7 (58.3)	10 (45.5)	17 (40.5)	31 (37.3)
Splenectomy	5 (41.7)	10 (45.5)	21 (50.0)	42 (50.6)

n (%)

Table 21. Efficacy by number of previous ITP treatments at the baseline (≤3, >3)
(Japanese study 20[redacted]0216) (partially modified from the submitted data)

Number of previous ITP treatments	≤3		>3	
	Placebo group (n = 5)	Romiplostim group (n = 10)	Placebo group (n = 7)	Romiplostim group (n = 12)
Number of weeks platelet response observed	0.4 ± 0.5 weeks	9.1 ± 3.7 weeks	0.0 ± 0.0 weeks	9.8 ± 3.1 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13	4200 ± 8800/μL	68,200 ± 29,100/μL	900 ± 4500/μL	144,200 ± 106,700/μL
Number of weeks platelet count in 50,000-200,000/μL	0.4 ± 0.5 weeks	6.3 ± 3.1 weeks	0.0 ± 0.0 weeks	6.3 ± 3.5 weeks

Mean ± SD

Table 22. Efficacy by number of previous ITP treatments at the baseline (≤3, >3)
(Foreign studies 20030105 and 20030212 pooled) (partially modified from the submitted data)

Number of previous ITP treatments	≤3		>3	
	Placebo group (n = 17)	Romiplostim group (n = 29)	Placebo group (n = 25)	Romiplostim group (n = 54)
Number of weeks platelet response observed	1.0 ± 2.0 weeks	7.8 ± 3.5 weeks	0.2 ± 0.6 weeks	6.3 ± 4.1 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13	17,000 ± 37,500/μL	107,600 ± 86,500/μL	900 ± 4500/μL	144,200 ± 106,700/μL
Number of weeks platelet count in 50,000-200,000/μL	0.8 ± 1.6 weeks	6.4 ± 3.5 weeks	0.2 ± 0.6 weeks	5.7 ± 3.9 weeks

Mean ± SD

PMDA considers as follows:
Although a sufficient number of patients were not included in the investigation, the data suggest that the efficacy of romiplostim can be provided irrespective of baseline ITP treatment history. However, when other treatment options are also available, appropriateness of romiplostim treatment should be carefully determined considering risk/benefit balance of each treatment option.

b) Splenectomy status at the baseline

The applicant explained as follows:
In the Japanese study 20[redacted]0216, the subjects splenectomized before the study participation accounted for 41.7% (5 of 12 subjects) in the placebo group and 45.5% (10 of 22 subjects) in the romiplostim group, and at the time of inclusion, 10.6 ± 6.9 years and 8.1 ± 6.8 years (mean ± SD) had passed since splenectomy in the respective groups above. In the Japanese study 20[redacted]0216, the number of weeks (mean ± SD) in which a positive platelet response (the platelet count being increased to ≥50,000/μL) was observed in the splenectomized sub-group was 0.0 ± 0.0 week in the placebo group and 9.7 ± 3.4 weeks in the romiplostim group, while that in the non-splenectomized sub-group was 0.3 ± 0.5 weeks and 9.3 ± 3.5 weeks in the respective groups; and the number of weeks (mean ± SD) in which the platelet count was in the range of 50,000 to 200,000/μL in the splenectomized sub-group was 0.0 ± 0.0 weeks in the placebo group and 6.6 ± 3.7 weeks in the romiplostim group, while that in the non-splenectomized sub-group was 0.3 ± 0.5 weeks and 6.1 ± 3.0 weeks, respectively. The change of the mean platelet count from the baseline, measured between Weeks 10 and 13, in the splenectomized sub-group was 2700 ± 3200/μL in the placebo group and 130,800 ± 112,800/μL in the romiplostim group, and that in the non-splenectomized sub-group was 1900 ± 8400/μL and 92,000 ± 61,500/μL, respectively. Of foreign studies, Study 20030105 was conducted in splenectomized ITP patients, and Study 20030212 in non-splenectomized ITP patients. In both studies, the platelet response occurred in more subjects in the romiplostim group than in the placebo group; the percentages of the subjects who achieved a durable platelet response and the subjects who achieved either a durable or transient platelet response were higher in the romiplostim group than in the placebo group; and the platelet response occurred for an extended period in the romiplostim group. Accordingly, the efficacy of romiplostim was confirmed irrespective of the splenectomy status in the foreign studies. Therefore, in both Japanese and foreign clinical studies, the efficacy of romiplostim was confirmed irrespective of the splenectomy status.

PMDA considers as follows:
Although a sufficient number of patients were not investigated, the data suggest that the efficacy of romiplostim can be provided irrespective of the splenectomy status. Since the dose of romiplostim is to be adjusted according to the platelet count, the difference in the efficacy of romiplostim between the splenectomized and non-splenectomized patients would not become a clinically relevant problem. However, since the clinical positioning of romiplostim in relation to splenectomy has not been established, when choosing a therapy for non-splenectomized patients, it should be noted that splenectomy may cure ITP while romiplostim is highly likely to be a long-term treatment. Appropriateness of romiplostim should be carefully considered according to patients' individual conditions and background.

c) Concomitant ITP therapy status at the baseline

The applicant explained as follows:
The efficacy data from the Japanese and foreign phase III studies (Japanese study 20[redacted]0216, Foreign study 20030105 and 20030212) were stratified by concomitant ITP therapy status at the baseline, and the results are shown in Tables 23 and 24. No large differences were found in the efficacy of romiplostim between the subgroups in any study. Accordingly, the efficacy of romiplostim can be expected irrespective of the concomitant ITP therapy status at the baseline.

Table 23. Efficacy by concomitant ITP therapy status at the baseline (Japanese study 20[redacted]0216) (partially modified from the submitted data)

Concomitant ITP therapy	Yes		No	
	Placebo group (n = 10)	Romiplostim group (n = 13)	Placebo group (n = 2)	Romiplostim group (n = 9)
Number of weeks platelet response observed	0.2 ± 0.4 weeks	10.2 ± 3.0 weeks	0.0 ± 0.0 weeks	8.4 ± 3.7 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13	2800 ± 6900/μL	103,100 ± 57,600/μL	-600 ± 4100/μL	119,100 ± 124,100/μL
Number of weeks platelet count in 50,000-200,000/μL	0.2 ± 0.4 weeks	7.2 ± 3.1 weeks	0.0 ± 0.0 weeks	5.0 ± 3.2 weeks

Mean ± SD

Table 24. Efficacy by concomitant ITP therapy status at the baseline (Foreign studies 20030105 and 20030212 pooled) (partially modified from the submitted data)

Concomitant ITP therapy	Yes		No	
	Placebo group (n = 15)	Romiplostim group (n = 30)	Placebo group (n = 27)	Romiplostim group (n = 53)
Number of weeks platelet response observed	0.9 ± 2.0 weeks	6.6 ± 4.1 weeks	0.3 ± 0.9 weeks	6.9 ± 3.9 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13 [a)]	18,100 ± 45,500/μL	83,500 ± 74,300/μL	3400 ± 11,600/μL	81,000 ± 66,200/μL
Number of weeks platelet count in 50,000-200,000/μL	0.7 ± 1.6 weeks	5.6 ± 3.9 weeks	0.3 ± 0.9 weeks	6.1 ± 3.8 weeks

Mean ± SD
a) Yes: 14 subjects in the placebo group, 28 subjects in the romiplostim group

PMDA considers as follows:
Although a sufficient number of patients were not included in the investigation, the data suggest that the efficacy of romiplostim can be provided irrespective of the concomitant ITP therapy status at the baseline. Although the dose of romiplostim can be adjusted by monitoring the platelet count, attention should be paid to an excessive increase of the platelet count if a therapy with a different mechanism is concomitantly given.

d) Platelet count at the baseline

The applicant explained as follows:
The efficacy data from the Japanese study 20[redacted]0216 and Foreign studies 20030105 and 20030212 were stratified by platelet count at the baseline (<10,000/μL, ≥10,000/μL), and the results are shown in Tables 25 and 26. In both Japanese and foreign studies, the efficacy of romiplostim was found irrespective of the baseline platelet count, and the efficacy of romiplostim tended to be greater with the higher baseline platelet count.

Table 25. Efficacy by platelet count at the baseline (Japanese study 20[redacted]0216) (partially modified from the submitted data)

Platelet count	<10,000/μL		≥10,000/μL	
	Placebo group (n = 3)	Romiplostim group (n = 5)	Placebo group (n = 9)	Romiplostim group (n = 17)
Number of weeks platelet response observed	0.0 ± 0.0 weeks	7.2 ± 6.1 weeks	0.2 ± 0.4 weeks	10.2 ± 1.8 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13	1500 ± 800/μL	96,200 ± 76,800/μL	2500 ± 7600/μL	113,600 ± 93,400/μL
Number of weeks platelet count in 50,000-200,000/μL	0.0 ± 0.0 weeks	5.4 ± 4.6 weeks	0.2 ± 0.4 weeks	6.6 ± 2.9 weeks

Mean ± SD

Table 26. Efficacy by platelet count at the baseline (Foreign studies 20030105 and 20030212 pooled) (partially modified from the submitted data)

Platelet count	<10,000/μL		≥10,000/μL	
	Placebo group (n = 13)	Romiplostim group (n = 21)	Placebo group (n = 29)	Romiplostim group (n = 62)
Percentage of the subjects with durable platelet response[a)]	0.0% (0/13)	28.6% (6/21)	3.4% (1/29)	56.5% (35/62)
Percentage of the subjects with overall platelet response[b)]	0.0% (0/13)	66.7% (14/21)	10.3% (3/29)	88.7% (55/62)
Number of weeks platelet response observed[c)]	0.1 ± 0.3 weeks	9.4 ± 8.0 weeks	1.1 ± 3.0 weeks	15.2 ± 7.2 weeks
Number of subjects with platelet response	7.7%(1/13)	85.7% (18/21)	27.6% (8/29)	91.9% (57/62)

a) Platelet response for at least 6 weeks of the last 8 weeks (Weeks 18 to 25) of the treatment period without salvage therapy
b) Subjects with durable platelet response or transient platelet response (transient response, at least 4 platelet responses between Weeks 2 and 25 without durable platelet response)
c) Mean ± SD

PMDA considers as follows:
Although a sufficient number of patients were not included in the investigation, the data suggest that the efficacy of romiplostim can be provided irrespective of the baseline platelet count. Since the greater efficacy tended to be observed in the subjects with higher baseline platelet count, the relevant information should be appropriately provided to healthcare providers in the clinical settings so that physicians will give due consideration to the risk of excessive platelet increase when giving romiplostim to patients with high baseline platelet count.

e) *H.pylori* eradication at baseline

Japanese chronic ITP patients are frequently tested positive for *H.pylori*, and the JGL recommends that *H.pylori* positive subjects preferentially undergo eradication. In consideration of this, PMDA asked the applicant to present the *H.pylori* infection and eradication statuses in the Japanese and foreign phase III studies (Japanese study 20[redacted]0216, Foreign studies 20030105 and 20030212) and then to explain the relationship of the efficacy of romiplostim with *H. pylori* infection and eradication statuses.

The applicant responded as follows:
The inclusion criteria in the Foreign studies 20030105 and 20030212 did not have the provision concerning history of *H.pylori* infection or eradication, and thus the investigation was not sufficiently implemented. In the Japanese study 20[redacted]0216, 25.0% (3 of 12 subjects) in the placebo group and 50.0% (11 of 22 subjects) in the romiplostim group had undergone *H.pylori* eradication before study participation. The data on the efficacy are as shown in Tables 27 and 28. In this study, the information about whether or not the eradication succeeded was not collected, and thus the infection status during the study treatment was unknown. However, the efficacy of romiplostim can be obtained irrespective of the infection or eradication status.

Table 27. Results of the efficacy by *H.pylori* eradication status (romiplostim group, Japanese study 20[redacted]0216) (partially modified from the submitted data)

H.Pylori eradication treatment	Yes (n = 11)	No (n = 11)
Number of weeks platelet response observed	9.6 ± 3.2 weeks	9.4 ± 3.6 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13	147,100 ± 107,500/μL	72,200 ± 42,400/μL
Number of weeks platelet count in 50,000-200,000/μL	5.9 ± 3.3 weeks	6.7 ± 3.3 weeks
Percentage of the subjects with platelet response	100%(11/11)	90.9% (10/11)
Median time to obtain platelet response	1.0 week	1.0 week

Mean ± SD

Table 28. Results of the efficacy by *H.pylori* eradication status (placebo group, Japanese study 20[redacted]0216) (partially modified from the submitted data)

H.Pylori eradication treatment	Yes (n = 3)	No (n = 9)
Number of weeks platelet response observed	0.7 ± 0.6 weeks	0.0 ± 0.0 weeks
Change of the mean platelet count from the baseline, measured between Week 10 and Week 13	8500 ± 10,300/μL	200 ± 3500/μL
Number of weeks platelet count in 50,000-200,000/μL	0.7 ± 0.6 weeks	0.0 ± 0.0 weeks
Percentage of the subjects with platelet response	66.7% (2/3)	0.0% (0/9)
Median time to obtain platelet response	11.0 weeks	-

Mean ± SD

PMDA considers as follows:
Although a sufficient number of patients were not included in the investigation, the data suggest that the efficacy of romiplostim can be provided irrespective of previous treatment history of *H.pylori* eradication. However, whether or not the *H.pylori* eradication was successful before initiation of treatment was unknown and a successful eradication may lead to remission of ITP. Therefore, there is not yet any clear evidence to strongly recommend the administration of romiplostim to *H.pylori* positive subjects.

Taking into account the investigations (a) to (d) above, PMDA has concluded, in the manner below, that at present, there are no baseline patient background factors that may compromise the efficacy of romiplostim in chronic ITP patients: the platelet count-increasing effect of romiplostim was observed in the romiplostim-treated patients in all clinical studies submitted; the effect was almost consistent irrespective of patient background factors that may affect the platelet count increase such as ITP treatment history, (concomitant or previous) ITP therapy, and platelet count at the baseline; romiplostim treatment can be expected to suppress haemorrhage symptom

through the increased platelet count; and the long-term study data demonstrated that the increased platelet count was maintained during the treatment with romiplostim.

4.(iii).B.(4) Safety

4.(iii).B.(4).1) Risk of thrombosis or thromboembolism

In general, an increased risk of thrombosis or thromboembolism is predicted when the platelet count exceeds the upper limit of the normal range (400,000/μL).

The applicant explained the risk of these adverse events during romiplostim treatment as follows: In the safety analysis consisting of the subjects who were included in the ITP Safety Set and received the study drug at least once (718 subjects: 653 subjects in the romiplostim-treated subset; 138 subjects in the non-romiplostim-treated subset), adverse events related to thrombosis or thromboembolism occurred in 39 of 653 subjects (6.0%, 69 events [7.5/100 patient-years]) in the romiplostim-treated subset and in 5 of 138 subjects (3.6%, 6 events [5.5/100 patient-years]) in the non-romiplostim-treated subset. In the romiplostim-treated subset, the major events (number of events) included deep vein thrombosis (11 events [1.2/100 patient-years]), pulmonary embolism (10 events [1.1/100 patient-years]), myocardial infarction (8 events [0.9/100 patient-years]), catheter related complication (6 events [0.7/100 patient-years]), and thrombophlebitis (5 events [0.5/100 patient-years]). The adverse event related to thrombosis or thromboembolism that occurred in the Japanese studies was transient ischaemic attack (1 event [1.9/100 patient-years]) in the romiplostim group. The platelet count (mean ± SD) at the time of onset of adverse events related to thrombosis or thromboembolism was 172,200 ± 214,900/μL in the romiplostim-treated subset and 150,800 ± 170,600/μL in the non-romiplostim-treated subset. Although the time of onset and platelet count were mostly considered unrelated, 6 subjects experienced thromboembolism-related adverse events when the platelet count excessively increased to above the discontinuation criterion (400,000/μL) or immediately after that.

PMDA asked the applicant to explain whether or not the safety concern would be raised if the discontinuation criterion of romiplostim treatment for the platelet count was set as 400,000/μL, which was considerably greater than the count requiring some therapeutic measures.

The applicant responded as follows:
The safety of romiplostim was evaluated in an analysis set consisting of the subjects who received the study drug at least once in the Phase 3 ITP Long-Term Safety Set and Japanese and foreign long-term extension studies (Japanese study 20[redacted]0113, Foreign study 20030213) (151 subjects in the romiplostim-treated subset, 54 subjects in the non-romiplostim-treated subset). In this analysis set, the adverse events related to thrombosis or thromboembolism occurred in 9 of 151 subjects (6.0%) in the romiplostim treated subset (15 events [4.9/100 patient-years]) and in 1 of 54 subjects (1.9%) in the non-romiplostim-treated subset (1 event [4.5/100 patient-years]). The occurrence of adverse events by platelet count at the time of onset in the romiplostim-treated subset was 0.2/100 weeks (7 of 3673 events) at a platelet count of <50,000/μL, 0.0/100 weeks (4 of 9581 events) at a platelet count range of ≥50,000/μL and <200,000/μL, 0.0/100 weeks (1 of 2302 events) at a platelet count range of ≥200,000/μL and <400,000/μL, and 0.6/100 weeks (3 of 531 events) at a platelet count of ≥400,000/μL, while that in the non-romiplostim-treated subset was 0.1/100 weeks (1 of 996 events) at a platelet count of <50,000/μL.

As described above, the occurrence of adverse events related to thrombosis or thromboembolism did not increase at a platelet count range of ≥200,000/μL and <400,000/μL, and no new events occurred in this range either. The safety could be ensured by setting dose adjustment rules as follows: when the platelet count exceeds 200,000/μL, the dose should be decreased by 1 μg/kg biweekly; when the platelet count exceeds 400,000/μL, the treatment with romiplostim should be discontinued. A clinical study of a TPO receptor agonist, a similar drug, in patients with chronic hepatic diseases, was prematurely terminated due to adverse events of thrombosis or thrombosis-

related adverse events and then the applicant investigated the adverse events in their studies by hepatic impairment status at the baseline. As a result, adverse events related to thrombosis or thromboembolism occurred in 35 of 561 subjects without hepatic impairment (6.2%, 60 events [7.5/100 patient-years]) and in 4 of 92 subjects with hepatic impairment (4.3%, 9 events [7.5/100 patient-years]).

PMDA considers as follows:
Since the incidence of thromboembolic adverse events was extremely low, even pooled data from the Japanese and foreign clinical studies of romiplostim were not enough for investigation of the relationship between the platelet count increased by romiplostim and thromboembolic adverse events as well as the increased risk of thromboembolism in patients with hepatic impairment. Accordingly, at present, it remains unclear how much increase in platelet count caused by romiplostim is enough to reduce the risk of thromboembolic adverse events in ITP patients or ITP patients with hepatic impairment. It is also unknown whether or not an excessive or rapid increase of the platelet count may cause thrombosis or thromboembolism. Based on the above, the platelet count increased by romiplostim should be kept at the minimum required level. The clinically appropriate target platelet count should be individually set according to the patient background, but the target upper limit ensuring the safety will be finalized, taking also account comments raised in the Expert Discussion. In addition, it is necessary to continue to collect information on the thromboembolic adverse events and platelet count at the time of onset via post-marketing surveillance etc., and then to appropriately provide the information.

4.(iii).B.(4).2) Rebound risk after discontinuation

PMDA asked the applicant whether or not the platelet count decreased due to a rebound and whether or not events suggesting an increased haemorrhage risk occurred after discontinuation of romiplostim.

The applicant responded as follows:
The platelet counts over time after discontinuation of romiplostim was investigated in 87 subjects who received romiplostim in the Japanese and foreign phase III studies and had their platelet counts measured at least once at 2 weeks after the final administration or later (Week 14 and thereafter in the Japanese studies, Week 26 and thereafter in the foreign studies). After the completion of the phase III studies, these patients were resumed romiplostim treatment by transfering to the long-term extension studies when the platelet count decreased to <50,000/μL, therefore the period for this investigation was cut off at the transfer. The platelet count decreased after the discontinuation in all of the subjects and then reached <50,000/μL within 2 weeks in approximately 60% of the subjects, within 3 weeks in approximately 80% of the subjects, and at ≥10 weeks in approximately 10% of the subjects. Furthermore, investigation of the change from the baseline to the last measured platelet count in each subject showed that the platelet count had decreased below the baseline level by >10,000/μL in 11 of 87 subjects (12.6%). As described above, the platelet count decreased after discontinuation of romiplostim, and there is a concern that a rebound might occur in some patients. The package insert, therefore, has included the caution statement that the platelet count will decrease after discontinuation and the instruction that the blood count should be measured weekly for at least the first 2 weeks after discontinuation of romiplostim. Furthermore, in the Foreign study 20030212, 1 subject who had been receiving an antiplatelet agent for treatment of cerebral thrombosis concomitantly with romiplostim died from haemorrhage intracranial (platelet count at the time of onset, 5000/μL) after discontinuation of romiplostim. In response to this event, the package insert has included the statement that in patients receiving an anticoagulant agent or antiplatelet agent, the haemorrhage risk will increase after discontinuation of romiplostim.

PMDA considers as follows:

The romiplostim treatment was to be resumed when the platelet count decreased to <50,000/μL in the long-term extension studies, and the investigation of the rebound above is not sufficient. A risk of rebound still cannot be ruled out since, as the applicant explained, the platelet count decreased to below the baseline level after discontinuation of romiplostim in some of the subjects. In addition, the platelet count decreased after discontinuation of romiplostim irrespective of whether or not the decrease was due to rebound. Accordingly, thorough attention will be required for the haemorrhage risk after discontinuation (treatment completion) of romiplostim. It is appropriate that the proposed package insert include the following caution statement: the platelet count should be measured weekly for at least the first 2 weeks after discontinuation of romiplostim; and attention should be paid to haemorrhage after discontinuation of romiplostim. Furthermore, it is necessary to include the caution statement about adverse drug reactions of haemorrhage, because 1 subject died from haemorrhage intracranial after discontinuation of romiplostim. In addition, since romiplostim has been only administered to an extremely limited number of Japanese ITP patients, it is necessary to collect the information on platelet count, haemorrhage adverse events, salvage therapy, etc., after the discontinuation via post-marketing surveillance. The measurement frequency of the platelet count after discontinuation, appropriateness of the cautions for haemorrhagic adverse events, and necessity of collecting post-marketing information will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(4).3) Risk of increased bone marrow reticulin or myelofibrosis

The applicant explained the risk of increased bone marrow reticulin or myelofibrosis caused by romiplostim as follows:

It has been reported that bone marrow reticulin is found in approximately 70% of healthy adult subjects (Kuter DJ et al. *Br J Haematolo.* 2007;139:351-62) as well as in approximately two thirds of no-romiplostim treated ITP patients (Mufti G et al. *Blood.* 2006;108:Abstract 3982). Increased reticulin in the bone marrow is considered to be caused by megakaryocytes excessively increased in the bone marrow by TPO and cytokines released by the platelets. In non-clinical studies in rats, myelofibrosis (special staining for reticulin and collagen not performed) was observed, but was confirmed to resolve following washout. In the ITP Safety Set (718 subjects), adverse events related to increased bone marrow reticulin occurred in 12 of 653 subjects (1.8%, 12 events [1.3/100 patient-years]) in the romiplostim-treated subset. These events included bone marrow disorder (10 events [1.1/100 patient-years]), myelofibrosis and myeloproliferative disorder (1 event each [0.1/100 patient-years]), but no such events occurred in any of 138 subjects in the non-romiplostim-treated subset. In the Japanese clinical studies, no adverse events related to increased bone marrow reticulin were reported. Separately from these subjects, 1 adverse event related to myelofibrosis of bone marrow disorder (types one and three collagen in marrow as described by the physician) was reported (1 event, 0.1/100 patient-years), but its causal relationship to romiplostim was ruled out. As described above, the risk of increased bone marrow reticulin or myelofibrosis could not be ruled out, and thus the risk of these events and examination for increased bone marrow reticulin will be cautioned in the package insert.

PMDA accepted the applicant's explanation and considered that the following caution statements are appropriate: attention should be paid to increased bone marrow reticulin or myelofibrosis; examination should be performed if development of these events is suspected; and if any abnormalities are observed, romiplostim should be discontinued and bone marrow examination should be performed. Furthermore, since the risk of increased bone marrow reticulin or myelofibrosis may increase with the extending treatment period, the post-marketing information about these adverse events should be continuously collected including data from the long-term treatment.

4.(iii).B.(4).4) Risk of hematological malignancy or MDS

The applicant explained the risk of hematological malignancy or MDS due to romiplostim as follows:

Theoretically, TPO receptor agonists are considered to stimulate proliferation of myeloid tumor cells through the TPO receptor mainly expressed on the surface of the bone marrow cells. Although there is no clear evidence that the interaction between romiplostim and TPO receptor generates proliferative signals in the myeloid leukemia cells and other neoplastic hematopoietic cells, TPO and rhuMGDF enhanced the proliferation of acute myeloid leukemia cells in the *in vitro* test system. In the ITP Safety Set (718 subjects), adverse events related to hematological malignancy or MDS occurred in 5 of 653 subjects in the romiplostim-treated subset (0.8%, 6 events [0.7/100 patient-years]) and in 2 of 138 subjects in the non-romiplostim-treated subset (1.4%, 2 events [1.8/100 patient-years]). The adverse events related to hematological malignancy or MDS in the romiplostim group included acute myeloid leukaemia, B-cell lymphoma, chronic lymphocytic leukaemia, lymphoma, myelofibrosis, and myeloproliferative disorder (1 event each [0.1/100 patient-years]). In the Japanese studies, no such adverse events occurred. On the other hand, in the foreign phase I/II study in MDS patients (Study 20050159), of 44 subjects in the Part A, transformation into acute myeloid leukaemia occurred in 2 subjects, transient blast cell count increased in 4 subjects, and chronic myelomonocytic leukaemia in 1 subject; transformation into acute myeloid leukaemia occurred in 1 of 28 subjects in the Part B. That is, although the incidence was low, hematological malignancy was reported in foreign clinical studies in ITP patients; transient blast cell count increased and transformation into AML were reported in the foreign clinical studies in MDS patients; and the cautions for hematological malignancy or MDS were provided in the foreign labeling. In consideration of the above, the relevant cautions have been included in the proposed Japanese package insert. Attention will be continuously paid to the post-marketing information about hematological malignancy or MDS, and if the information for which a relationship to romiplostim cannot be ruled out is obtained, the content will be reviewed and actions such as revision of the package insert will be taken where necessary.

PMDA considers as follows:

The relationship between romiplostim and risk of hematological malignancy or MDS in ITP patients has not been sufficiently clarified because the currently available information is limited due to the low incidence of the events related to hematological malignancy or MDS. However, it is appropriate to provide cautions for potential of the adverse events based on the mechanism of action of romiplostim and foreign study data. Post-marketing information on the events including data from the long-term treatment should be collected via post-marketing surveillance, and the relevant information should be appropriately provided. In addition, distinguishing ITP from MDS can be difficult especially in patients with decreased platelet count. Therefore, cautions to the following effect should be appropriately provided: romiplostim should not be administered unnecessarily for an extended period and appropriate differential diagnosis must be made, taking into account the possibility of the other diseases than ITP if romiplostim is considered ineffective.

4.(iii).B.(4).5) Safety of romiplostim in special populations

4.(iii).B.(4).5).(a) Patients with renal or hepatic impairment

Although the proposed package insert does not include cautions for patients with renal impairment or hepatic impairment, PMDA considers as follows:

Although the data from a clinical study in subjects with renal impairment have not been included in the application dossier, non-clinical study data suggested that contribution of renal excretion becomes greater when a higher dose of romiplostim is given [see "3.(ii).B.(2) Contribution of kidneys to excretion of romiplostim"]. Since the serum romiplostim concentration might be increased in patients with renal impairment, and romiplostim has never been administered in patients with renal impairment, it is necessary to provide the caution for careful administration. As with the renal impairment, it is necessary to provide the caution for careful administration to

patients with hepatic impairment, who have never received romiplostim in the clinical studies, taking account that it has been reported that similar drugs might raise the risk of thrombosis in such patients. Necessity of cautions for patients with renal impairment or hepatic impairment will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).5).(b) Use in pregnant women

In consideration that the platelet count may have to be controlled during pregnancy and delivery in chronic ITP patients, PMDA asked the applicant to explain the appropriateness of romiplostim treatment in pregnant women or in women who may possibly be pregnant.

The applicant explained as follows:

Reproductive and developmental toxicity studies suggested that romiplostim crossed maternal placenta, and increases in fetal resorption, fetal platelet count, and neonatal death rate were noted. Therefore, the proposed package insert has included a caution that this drug should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Although excretion of romiplostim into human milk has not been investigated, it is known that human IgG is excreted into milk. Romiplostim has the Fc region of IgG in its structure and the excretion into milk cannot be completely ruled out. Accordingly, to ensure the safety in suckling infants, the proposed package insert has included the following statement: it is preferable to avoid administration of romiplostim to nursing mothers, and if it is inevitable, nursing mothers should discontinue breast-feeding.

PMDA considers as follows:

Romiplostim might cross maternal placenta, and increases in fetal resorption, fetal platelet count, and neonatal death rate were noted. Therefore, it is necessary to provide sufficient cautions and to collect the information on the treatment in pregnant women via post-marketing surveillance.

4.(iii).B.(5) Indication

The proposed indication was thrombocytopenia in adult chronic immune-mediated (idiopathic) thrombocytopenic purpura, and the proposed precautions for indications was as follows: the product may be used in patients with thrombocytopenia in adult chronic immune-mediated (idiopathic) thrombocytopenic purpura only in whom corticosteroid therapy has not been sufficiently effective or cannot be continued due to the adverse drug reactions, or in whom corticosteroid therapy is contraindicated.

The applicant explained the evidence for the above proposals as follows:

In the Japanese and foreign phase III studies in adult chronic ITP patients with ITP treatment history including at least 1 type of medication, most of the subjects (100% in the Japanese study [34 of 34 subjects], 94.4% in the foreign studies [118 of 125 subjects]) previously received corticosteroids. In each study, the patients with the low platelet count who had not sufficiently responded to corticosteroids were included. However, even in such patients, the efficacy and safety of romiplostim were observed.

PMDA considers as follows:

The Japanese and foreign clinical studies showed clinically significant efficacy and clinically acceptable safety of romiplostim in each study population. Accordingly, it is appropriate to specify the intended patients of the product in the indication based on the subject backgrounds in these clinical studies, but that does not suggest rejecting use of romiplostim in patients in whom the other treatment options cannot be used due to tolerability or other reasons in clinical settings. Based on the above discussion and the statements of the approved drugs intended for similar patients to those of romiplostim, it is appropriate to specify the indication as chronic idiopathic thrombocytopenic purpura, and to provide the following cautions in the Precautions for Indications section: this drug should be used when the other treatment options are not sufficiently

effective or have limitations due to tolerability; the drug should be used when a haemorrhage risk is determined to be high based on the platelet count and clinical symptoms. However, the appropriateness of the indications will be finalized, taking also account of comments raised in the Expert Discussion.

4.(iii).B.(6) Dosage and administration

4.(iii).B.(6).1) Appropriateness of proposed dosage and administration

The following dosage and administration were proposed.

The initial dose for adults is 1 μg/kg (based on body weight) as Romiplostim (Genetical Recombination) administered subcutaneously once weekly. Then, the dose may be adjusted with reference to the following table so that the platelet count can be maintained within the target range of 50,000 to 200,000/μL. The maximum dose is 10 μg/kg per dose.

Dose adjustment table

Platelet count	Dose adjustment
<50,000/μL	Increase the dose weekly by 1 μg/kg.
>200,000/μL	Decrease the dose by 1 μg/kg biweekly if the platelet counts are within this range for 2 consesecutive weeks.
>400,000/μL	Suspend the administration. Resume the administration at the dose decreased by 1 μg/kg if the platelet count has decreased to ≤200,000/μL.

4.(iii).B.(6).1).(a) Initial dose

The applicant explained the rationale for the initial dose of romiplostim as follows:
In the Japanese phase III study (Study 20[redacted]0216) in which the starting dose of 3 μg/kg was chosen, the platelet count excessively increased to above the level for discontinuation of treatment (platelet count, 400,000/μL) by Week 3 in the early treatment phase in 6 of 22 subjects (27.3%) in the romiplostim group. In order to avoid the risk of thrombosis and thromboembolism, the initial dose for Japanese patients was also chosen to be 1 μg/kg, the same dose for foreign patients, while it is considered to achieve similar platelet count increase and to keep the count within the target range for Japanese patients with dose adjustment thereafter, judging from the following study results. The initial dose of 1 μg/kg with the appropriate dose adjustment thereafter depending on individual patient's platelet count was thus considered appropriate for Japanese patients.

- The Japanese phase II study (Study 20050162) demonstrated that romiplostim increases the platelet count dose-dependently in Japanese subjects, too.
- No marked differences were observed between the intrinsic factors of Japanese and foreign subjects. The extrinsic factors differed in terms of ITP treatment history, but the efficacy of romiplostim was confirmed irrespective of the ITP treatment history without safety concerns. Accordingly, the foreign study data can be used as reference.
- In the Japanese study (Study 20[redacted]0216) in which the initial dose of 3 μg/kg was chosen, the platelet count excessively increased immediately after initiation of treatment compared with the foreign studies (Studies 20030105 and 20030212) in which the initial dose of 1 μg/kg was chosen, but the incidence of adverse events was similar.
- The platelet counts over time and the incidence of adverse events in the foreign study (Study 20060131) in which the initial dose of 3 μg/kg was chosen were similar to those in the Japanese studies (Studies 20[redacted]0216 and 20[redacted]0113).
- In the foreign studies in which the initial doses of 1 μg/kg (Studies 20030105 and 20030212) and 3 μg/kg (Study 20060131) were chosen, the platelet count after the

dose adjustment remained within the target range. The maintenance level of the platelet count differed because the adjusted doses were different among studies due to different dose adjustment procedures, and the platelet count was maintained around 100,000/μL in the Study 20030212 and 180,000/μL in the study 20060131. No significant differences were observed among the safety profiles.

PMDA considers as follows:
The data at the initial dose of 1 μg/kg in Japanese patients are not available. In essence, a clinical study with the potentially appropriate dosage and administration should be conducted to demonstrate the efficacy and safety with the dosage and administration. The initial dose of 1 μg/kg is appropriate for the following aspects: ITP is a rare disease with a limited number of patients; foreign studies with the dosage and administration in which the initial dose was set at 1 μg/kg demonstrated the efficacy and safety of romiplostim; no differences in intrinsic or extrinsic ethnic factors that might affect the efficacy and safety of romiplostim were revealed between Japanese and foreign subjects, suggesting that the foreign study data could be used as reference to some extent; it is considered reasonable that the initial dose of 1 μg/kg based on the foreign study data is preferable to 3 μg/kg set in the Japanese studies to avoid excessive platelet count increase, which can raise the safety concern; and as the dose is to be adjusted according to the platelet count after the initiation of romiplostim treatment, the efficacy of romiplostim can be expected even with the low starting dose. However, it is necessary to collect the post-marketing information on the platelet counts over time after the initiation of romiplostim treatment and to provide the information to the healthcare providers in clinical settings promptly.

4.(iii).B.(6).1).(b) Maximum dose
The applicant explained the rationale for the maximum dose of romiplostim as follows:
In the foreign long-term extension study (Study 20030213), the maximum dose of 30 μg/kg was chosen when the study was started. However, the data accumulated during the study showed that the percentage of subjects with platelet response at the dose of >10 μg/kg was not higher than that at the dose of ≤10 μg/kg, and thus in the subsequent foreign studies, the maximum dose was changed to 10 μg/kg. In the Japanese phase III study (Study 20[redacted]0216) and Japanese extension study (Study 20[redacted]0113), the maximum dose of 10 μg/kg was chosen as with the foreign studies. In the Study 20[redacted]0216, no subjects received romiplostim at the dose of 10 μg/kg, but in the Study 20[redacted]0113, 8 of 44 subjects (18.2%) received it at the dose of 10 μg/kg. Of the 8 subjects, 5 subjects showed the platelet count increase to ≥50,000/μL and 2 subjects to >20,000/μL, and continued the treatment, but 1 subject did not show the increase and discontinued the treatment. In the 8 subjects who received romiplostim 10 μg/kg, no adverse events leading to study drug discontinuation were reported, and 1 subject experienced a serious adverse event (appendicitis) after administration of 10 μg/kg, but the causal relationship was ruled out. As described above, the maximum dose could be set at 10 μg/kg.

PMDA accepted the applicant's explanation and concluded that the maximum dose can be set at 10 μg/kg. However, the number of the subjects who received romiplostim 10 μg/kg in the Japanese studies is limited, and it is necessary to collect the information on the safety and efficacy at the dose of 10 μg/kg via post-marketing surveillance.

4.(iii).B.(6).1).(c) Target platelet count

The applicant explained the rationale for the target platelet count during the romiplostim treatment as follows:

The lower limit of 50,000/μL is defined as the level requiring no treatment according to the Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia (ITP) issued by the American Society of Hematology (George JN et al. *Blood.* 1996;88:3-40). It was thus set as the level that could avoid bleeding tendency and haemorrhagic risk. The upper limit of 200,000/μL is defined as a level which is well below the upper limit of normal range (400,000/μL) to proactively avoid the risk of thrombosis and thromboembolism due to otherwise higher-than-the-normal-limit platelet count possibly caused by the platelet count changes and excessive increase that occurred in ITP patients who had received multiple doses of romiplostim. No considerable safety concerns were raised in any of the phase III or long-term extension studies in or out of Japan to which the above setting was applied and the applicant considers such a setting appropriate.

PMDA considers as follows:

The target platelet count in ITP patients should be determined individually in consideration of their background. In particular, the upper limit in patients in whom the platelet count has been maintained at >50,000/μL should be set to the minimally required level in consideration of the safety. The target platelet count and dose adjustment procedure provided by the applicant were set as the dose adjustment rules in clinical studies, and thus it is not appropriate to uniformly specify 50,000 to 200,000/μL as the target value in the dosage and administration as proposed by the applicant. The concept of the target platelet count will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(6).1).(d) Dose adjustment table

The applicant explained the rationale for the dose adjustment table as follows:

In the Japanese studies, it was specified that the dose of romiplostim should be increased by 1 μg/kg biweekly when the platelet count was ≥10,000/μL and <50,000/μL, but the applicant considered it more appropriate to increase the dose of romiplostim by 1 μg/kg weekly because the platelet count would be monitored weekly at the same time as romiplostim treatment. In the course of Japanese long-term extension study (Study 20[redacted]0113), the increment at the platelet count <50,000/μL was changed from 2 μg/kg to 1 μg/kg, considering that the smaller increment might reduce the risk of excessive platelet count increase. As described above, it is appropriate to specify the increment at 1 μg/kg uniformly at the platelet count <50,000/μL in the dose adjustment table.

PMDA asked the applicant to explain whether or not weekly dose increase is appropriate in consideration that the platelet count started increasing 7 to 9 days after the romiplostim administration and reached the maximum between 11 and 15 days after administration.

The applicant explained as follows:

In the foreign phase I study in healthy adult subjects (Study 20000109), the platelet count reached the maximum on Days 11 to 15, but the studies in adult chronic ITP patients (Studies 20000137A, 20000127B, and 20010218, Study 20000137B) showed that the platelet count did not reach 50,000/μL in most of the patients, requiring additional dose on Day 15 or 22, and the inter-individual variability was large in response. These study data suggested that the dosing interval of 1 week, instead of 2 weeks, would be appropriate so as to increase the platelet count to ≥50,000/μL and maintain this level. The dose adjustment rules in the Japanese and foreign studies were complicated, and it was desirable to modify the rules into a simpler dose adjustment table while keeping the principle of the increasing criteria unchanged for the purpose of avoiding the dose adjustment errors in clinical practice. Furthermore, to reduce the haemorrhage risk earlier, it is appropriate to increase the dose by 1 μg/kg weekly as long as the platelet count is <50,000/μL for the following reason: until the platelet count increases to ≥50,000/μL, no rapid increase of the

platelet count has been observed, although the dose increase interval of 1 week leads to an increased next dose of romiplostim being administered before the maximum platelet count that the previous doses alone could give rise to.

PMDA considers it possible to set the increment at 1 μg/kg for patients with the platelet count <50,000/μL, because there are no clinical study data showing that the dose increase by 1 μg/kg in ITP patients with the platelet count <50,000/μL would result in an excessive increase far beyond 50,000/μL, although therapeutic results under the proposed dose adjustment table are not available in Japanese patients. In addition, it is unnecessary to uniformly reject the dose increase interval of 1 week, provided that careful judgment for dose increase is made under supervision and thorough observation of physicians with adequate knowledge and experience in ITP therapy. However, it is necessary to collect the post-marketing information on the platelet counts over time following the weekly dose increase in Japanese patients and provide the information to healthcare providers in the clinical settings promptly. The applicant proposed that the dose would not be decreased until the platelet count exceeded 200,000/μL, but the dose should be decreased if possible regardless of the rule, taking the individual patient background into account, to keep the platelet count at the minimum level required for the individual patients as described above, as long as the platelet count is maintained at >50,000/μL.

PMDA asked the applicant to explain the rationale for the rule for resuming after washout set by the applicant as follows: resume the administration at the dose decreased by 1 μg/kg when the platelet count is decreased to ≤200,000/μL.

The applicant responded as follows:
In the Japanese and foreign phase III studies, the platelet count increased to >400,000/μL in 26 of 105 subjects during the treatment period (18 of 83 subjects in the foreign studies, 8 of 22 subjects in the Japanese study). The platelet counts over time after washout in 14 subjects (6 subjects in the foreign studies, 8 subjects in the Japanese study) excluding subjects who received the emergency measures aiming at the platelet count increase (e.g. IVIG) were investigated. After the washout, the treatment was resumed according to the dose adjustment rule. The platelet counts (mean ± SD) immediately before and at week 1 after resuming were 77,500 ± 54,400/μL and 112,400 ± 115,000/μL, respectively, and the change was 34,900 ± 109,900/μL. The platelet count exceeded 400,000/μL in 1 subject at Week 1after resuming. In the long-term extension studies, the treatment was also controlled with similar settings, and no safety concerns were reported. To make the description in the package insert more specific, it will be revised as follows: resume the administration at the dose decreased by 1 μg/kg from that immediately before discontinuation when the platelet count is decreased to ≤200,000/μL.

PMDA considers that the platelet count can generally be controlled with the rule for resuming after washout as set by the appliant. However, a rapid platelet count increase occcurred in some subjects and thorough cautions should be provided to ensure careful follow-up after resuming.

As described above, PMDA considers the following actions appropriate: the dosage and administration of romiplostim are set as shown below; and the reference platelet count for dose adjustment serves only as a guide at present in accordance with the setting applied to the clinical studies and will be provided as a caution in the Precautions for dosage and administration. The dosage and administration of romiplostim will be finalized, taking account of comments raised in the Expert Discussion.

Dosage and administration:
The usual initial adult dosage is 1 μg/kg of Romiplostim (Genetical Recombination) administered subcutaneously. After the initiation of treatment, the dose may be adjusted according to the

platelet counts over time, and it should be injected subcutaneously once weekly. The maximum dose is 10 μg/kg once weekly.

Precautions for dosage and administration:

(1) The dose of romiplostim should be adjusted in accordance with 1) to 5) below.
    1) The product should be used at the minimum dose required therapeutically.
    2) The dose should be increased by 1 μg/kg when the platelet count is <50,000/μL.
    3) Decrease in the dose should be considered to the minimum level required therapeutically to reduce the haemorrhage of when the platelet count is in the range of 50,000/μL to 200,000/μL.
    4) The dose should be decreased by 1 μg/kg when the platelet count is in the range of 200,000/μL to 400,000/μL.
    5) The product should be discontinued when the platelet count exceeds 400,000/μL. If the platelet count is decreased to ≤200,000/μL after discontinuation, administration should be resumed at the dose decreased by 1 μg/kg from that before discontinuation.
(2) The rest is omitted.

4.(iii).B.(6).2) Discontinuation criteria for non-responders to romiplostim

The applicant explained the discontinuation criteria for non-responders to romiplostim as follows:
The Precautions for dosage and administration section of the package insert includes the following statement: When the platelet count does not increase to the level at which the clinically significant haemorrhage risk can be avoided even after 4 consecutive weekly treatments at the maximum dose of 10 μg/kg, appropriate measures such as discontinuation should be taken. The setting above is based on experiences in the Japanese and foreign long-term extension studies where romiplostim was to be discontinued for the subjects with the platelet count ≤20,000/μL even after 4 consecutive weekly treatments at the maximum dose of 10 μg/kg (except for the patients in whom the platelet count is ≤20,000/μL, but the romiplostim treatment is expected to reduce the bleeding tendency or haemorrhage risk).

PMDA considers that the romiplostim treatment should be discontinued promptly for patients in whom the platelet count is unlikely to increase to the level at which the haemorrhage risk can be avoided, and that there is no basis for considering that the response cannot be determined until romiplostim is administered at the maximum dose for 4 weeks. The period necessary to determine a patient to be a non-responder to romiplostim will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(6).3) Measurement interval of platelet count during romiplostim treatment

The applicant explained the measurement interval of platelet count during romiplostim treatment as follows:
The Precautions for dosage and administration section of the package insert includes the following statement: the platelet count should be measured weekly until the count is stabilized (the platelet count remains ≥50,000/μL for at least 4 weeks without dose adjustment) during romiplostim treatment; the platelet count should be measured once every 4 weeks even for the patients with a stable platelet count.

PMDA considers as follows:
After the initiation of romiplostim treatment, the platelet count increased 7 to 9 days after administration and reached the maximum at 11 to 15 days after administration in the Japanese and foreign long-term extension studies under the applicant's proposed settings. The platelet counts over time during their increase shortly after administration did not reveal any abnormalities in the other studies either and dose adjustments of romiplostim at the interval set by the applicant were satisfactory. In consideration of the above and feasibility in clinical practice in Japan, the following measurement protocol proposed by the applicant is almost appropriate only as a guide

for ensuring the safety: after the romiplostim treatment is started at the dose of 1 μg/kg in chronic ITP patients with a platelet count of <50,000/μL, the platelet count should be monitored weekly until the stabilized platelet count is achieved at the maintenance dose and then at least once every 4 weeks. It is necessary to determine the monitoring frequency of the platelet count on an individual basis and not uniformly. The above conclusion and appropriateness of the criteria for the stabilized platelet count will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(7) Others

4.(iii).B.(7).1) Function of platelets increased by romiplostim

The applicant explained the function of platelets increased by romiplostim as follows:
In the Japanese phase I study in healthy adult subjects (Study 20040134), the platelet aggregation rate was measured in the presence of ADP and collagen, and no marked differences were revealed in the measured rate between the placebo group and all romiplostim groups. In a literature (Gardiner et al. *Br J Haematol.* 2010;49:625-8), the platelet aggregation rate measured in ITP patients after 6 months of romiplostim treatment was reported, showing that romiplostim induced collagen aggregation and expressed the collagen receptor on the platelet surface to the similar extent as found in healthy adult subjects. Based on the above, even in ITP patients, platelets produced following the romiplostim treatment are also considered to have a normal function.

PMDA considers as follows:
Although the platelets increased by romiplostim function normally, there is no evidence ensuring that the platelet function is kept normal permanently in patients regularly administered romiplostim. Thus it is necessary to pay attention to whether or not the haemorrhage risk is increased even if the platelet count is maintained within the target range in patients who are to receive romiplostim for a substantial part of their lifetime.

4.(iii).B.(7).2) Effect of romiplostim on anti-platelet antibody

The applicant explained the effect of romiplostim on development or increase of anti-platelet antibody as follows:
There are no reports suggesting that romiplostim increased anti-platelet antibody, resulting in a decrease in platelet count. In the foreign phase III studies (Studies 20030105 and 20030212), antibodies against GPIa/IIa, GPIIb/IIIa, and GPIb/IX were measured (semi-quantitatively). No significant changes were noted in antibody load per unit blood volume before and after the initiation of romiplostim treatment, suggesting that romiplostim did not increase anti-platelet antibody.

Although there is no data suggesting that romiplostim is related to anti-platelet antibody production, PMDA considers it necessary to pay thorough attention to a rapid decrease in platelet count during romiplostim treatment and perform periodic tests without fail, since the number of patients investigated is limited.

4.(iii).B.(7).3) Effect of neutralizing antibody on the efficacy and safety of romiplostim

The applicant explained development of neutralizing antibody due to romiplostim as follows:
As of September 2010, 14 clinical studies had been conducted in healthy adult subjects and ITP patients, of whom 78 healthy adult subjects and 560 ITP patients were subjected to an antibody test. Of these, 2 subjects were tested positive for neutralizing antibody against romiplostim, but not against TPO. In any subject who tested positive for neutralizing antibody against romiplostim, the next test result was negative; the occurrence of the neutralizing antibody was reversible. In 1 subject, the platelet count decreased transiently during occurrence of the neutralizing antibody, suggesting that the occurrence affected the efficacy of romiplostim. In this subject, severe worsening of ITP occurred as an adverse event. Production of neutralizing antibody against romiplostim may attenuate its effects, making it difficult to maintain the platelet count, and

romiplostim treatment should be discontinued. As a post-marketing measure, the caution will be provided that production of neutralizing antibody should be suspected in the following cases: when the response to romiplostim is reduced; or when it becomes difficult to maintain the platelet count. The antibody test should be performed if the attending physician considers it necessary. To test the antibody, screening with biosensor immunoassay should be firstly performed, and only for the positive samples, neutralizing antibodies against romiplostim and TPO should be measured by the bioassay method.

Since occurrence of neutralizing antibody against romiplostim attenuates the efficacy of romiplostim and affects the ITP therapy with romiplostim, PMDA considers the following measures appropriate: thorough cautions and information are provided via package insert; and a post-marketing system is established to ensure that the test is performed promptly wherever necessary and that necessary information is provided to healthcare providers in clinical settings. In addition, PMDA considers it important to ensure that healthcare providers are thoroughly informed of such a system.

4.(iii).B.(8) Post-marketing surveillance

The applicant explained post-marketing surveillance for romiplostim as follows:

Post-marketing surveillance will be implemented to confirm the safety and efficacy of long-term treatment with romiplostim (1 year) under routine use in all patients who start receiving romiplostim treatment within 2 years after market launch of romiplostim. The priority investigation items planned are as follows: worsening of thrombocytopenia and haemorrhage-related events after discontinuation of romiplostim; and adverse drug reactions classified into the Blood and lymphatic system disorders (including thrombocytosis, thrombosis/thromboembolism, haemorrhage). The surveillance will include all patients who start romiplostim treatment within 2 years after market launch. The rationale for the target patients is as follows: of the priority investigation items, approximately 600 patients are necessary to detect 1 adverse drug reaction with the low incidence (e.g., thrombophlebitis, 0.5%) with 95% probability; and approximately 800 patients are expected to provide relevant medical information within 2 years. The follow-up period was set at 1 year because in the foreign long-term extension study (Study 20030213) 222 subjects were receiving the treatment (median treatment period, 48 weeks) at the interim tabulation time point of [redacted], 20[redacted]; there were no adverse drug reactions for which the incidence increased with the extended period of treatment or which were newly reported by ≥2 subjects after 48 weeks of the treatment.

PMDA considers as follows:

The priority investigation items provided by the applicant were largely appropriate. However, the currently available experience with romiplostim treatment in Japanese ITP patients is quite limited, and the proposed dosage and administration of romiplostim are different from those in the Japanese studies. Therefore, it is necessary to implement the surveillance in all ITP patients treated with romiplostim (all patient surveillance). In addition, it is important to examine whether or not patients inappropriate for romiplostim to be administered can be predicted by setting the patient background as investigation items. The long-term treatment may raise concerns such as elevated risk of increased bone marrow reticulin or myelofibrosis, hematological malignancy or MDS, thus, it is necessary to collect the information on the safety of long-term treatment (>1 year). The exercise of all patient surveillance and appropriateness of the plan will be finalized, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.4.2-4, 5.3.5.1-3, 5.3.5.2-2). As a result, protocol violations (noncompliance with the dose adjustment rules for study drug) and inconsistency between the source documents and case report form (no entry of adverse events) were found at some clinical study sites. In addition, the monitoring record was found to have no entry of the fact that the sponsor confirmed the above inconsistency between the source documents and case report form with the investigator. However, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of romiplostim in patients with chronic idiopathic thrombocytopenic purpura (ITP) has been demonstrated, and its safety is acceptable in view of its observed benefits. The product is a thrombopoiesis stimulating factor that activates the TPO receptor and enhances production of platelets and is considered to be a useful drug for patients with chronic ITP who are resistant to or cannot tolerate existing therapies. Still, further consideration will be needed concerning appropriateness of the dosage and administration and cautions, as well as items to be investigated after the market launch. Post-marketing surveillance should be implemented in all patients.

PMDA considers that romiplostim may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

November 17, 2010

I. Product Submitted for Registration

[Brand name]	Romiplate for Subcutaneous Injection (planned to be changed to Romiplate for S.C. Injection 250 μg)
[Non-proprietary name]	Romiplostim (Genetical Recombination)
[Applicant]	Kyowa Hakko Kirin Co., Ltd.
[Date of application]	March 29, 2010

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Clinical positioning and indication

PMDA made the following conclusions concerning the clinical positioning of romiplostim: it is a drug that may be chosen when further treatment is indicated for chronic ITP after the standard treatment and it can serve as one therapeutic option comparable to splenectomy based on the submitted clinical study data; for patients with difficulty in receiving corticosteroids, it may be used as long as the benefit is expected to outweigh the risk in consideration of the seriousness of the target disease, although it cannot be strongly recommended. The above conclusions of PMDA were discussed at the Expert Discussion. The following comments were raised from expert advisors: the PMDA's conclusions were appropriate; use of romiplostim prior to corticosteroids might not have to be ruled out as corticosteroids were frequently associated with adverse drug reactions; and it should be avoided to allow the use of romiplostim prior to corticosteroids without restrictions as the evidence supporting such use was not sufficient. However, these comments did not reject the PMDA's conclusions. They were thus supported finally. Furthermore, PMDA concluded that it is appropriate to specify the indication as chronic idiopathic thrombocytopenic purpura, and to provide the following cautions in the Precautions for Indications section of the package insert: the product should be used when the other treatment options are not sufficiently effective or have limitations due to tolerability; the product should be used when a haemorrhagic risk is judged to be high based on the platelet count and clinical symptoms. This conclusion was also finally supported by the expert advisors.

Taking the above discussions into account, PMDA has concluded that the following statement should be included in the Indication and Precautions for Indications sections of the package insert.

<u>Indication</u>
Chronic idiopathic thrombocytopenic purpura

<u>Precautions for Indications</u>
(1) The product should be used when the other treatment options are not sufficiently effective or have limitations due to tolerability.
(2) The product should be used when a haemorrhage risk is judged to be high based on the platelet count and clinical symptoms.

2. Dosage and administration and precautions for dosage and administration

(1) Dosage and administration

Expert advisors commented that the clinical study data in Japanese patients with the initial dose of 1 μg/kg were not available and that the rationale for the initial dose of 3 μg/kg in the Japanese phase III study was not sufficient. However, taking account of the relationship of the dosage and administration in the Japanese and foreign studies with the platelet counts over time as well as romiplostim-specific regimen characterized by dose adjustment according to the platelet count, expert advisors supported the PMDA's conclusion of admitting the following dosage and administration of romiplostim as appropriate: the usual initial adult dosage is 1 μg/kg of Romiplostim (Genetical Recombination) administered subcutaneously; after starting the treatment, the dose may be adjusted according to the platelet counts over time; it should be injected subcutaneously once weekly; and the maximum dose is 10 μg/kg once weekly. Concerning the proposed dosage and administration that included the dose adjustment procedure according to the platelet count, the following conclusion of PMDA was supported by the expert advisors: it would be difficult to specify the dose adjustment procedure uniformly without consideration of individual patient background and the reference platelet count for the dose adjustment is only a guide in accordance with the setting applied to clinical studies, therefore, such a matter should be provided as a caution in the Precautions for dosage and administration.

Taking the above discussion into account, PMDA has concluded that the following statement should be included in the Dosage and Administration section of the package insert.

Dosage and administration:
The usual initial adult dosage is 1 μg/kg of Romiplostim (Genetical Recombination) administered subcutaneously. After starting the treatment, the dose may be adjusted according to the platelet count and other patient's conditions, and it should be injected subcutaneously once weekly. The maximum dose is 10 μg/kg once weekly.

Expert advisors commented that attention should be paid to whether or not the dose setting based on the body weight would be appropriate even for obese patients. However, the information on the efficacy and safety in obese patients obtained from the previous clinical study data and foreign post-marketing data are limited. PMDA has thus concluded that the dose would be set based on the body weight even in obese patients at present, and the relevant information should be collected continuously via post-marketing surveillance.

(2) Precautions for dosage and administration

As examination of the dose adjustment rules in the Japanese and foreign studies and platelet counts over time suggested a risk of an unnecessary increase of the platelet count, taking the reduction of such risk into account, PMDA has concluded the following dose adjustment criteria are acceptable: the dose increase interval is set at 1 week, and the dose can be increased by 1 μg/kg in patients with the platelet count <50,000/μL, although careful judgment has to be made under the supervision and thorough observation of physicians with adequate knowledge and experience in ITP therapy. PMDA considers that although the platelet count as the guide for the dose adjustment may have to be based on the setting applied in clinical studies, the dose should be kept at the minimal level required in consideration of individual patient background once the platelet count has reached and been maintained at >50,000/μL. Therefore, the following dose adjustment procedures are considered appropriate: the dose should be not only maintained but also considered to be reduced; the dose should be decreased by 1 μg/kg when the platelet count is ≥200,000/μL; administration should be discontinued when the platelet count is >400,000/μL; administration should be resumed at the dose decreased by 1 μg/kg from that before discontinuation if the platelet count is decreased to ≤200,000/μL after discontinuation, and patients should be carefully observed. PMDA has concluded that the above cautions are

appropriate and should be included in the Precautions for dosage and administration section of the package insert as shown below.

Precautions for dosage and administration:

(1) The dose of romiplostim should be adjusted in accordance with 1) to 5) below.
   1) The product should be used at the minimum dose required therapeutically.
   2) The dose should be increased by 1 μg/kg when the platelet count is <50,000/μL.
   3) Decreasing the dose should be considered to the minimum level required therapeutically to reduce the risk of haemorrhage when the platelet count is in the range of 50,000/μL to 200,000/μL.
   4) The dose should be decreased by 1 μg/kg when the platelet count is in the range of 200,000/μL to 400,000/μL.
   5) The product should be discontinued when the platelet count exceeds 400,000/μL. Resume the administration at the dose decreased by 1 μg/kg from that before discontinuation if the platelet count has decreased to ≤200,000/μL after discontinuation.

The above conclusions of PMDA were discussed and comments raised from expert advisors were as follows: the PMDA's conclusions were appropriate; it is appropriate to adjust the platelet count to the minimum level required according to the individual patient as the platelet count maintained at 50,000/μL is sufficient for daily living, and that ≥100,000/μL is sufficient for haemorrhage control even during delivery or open surgery, but the dose determination would be difficult without a guide. Finally PMDA's conclusions were supported.

In consideration of these discussions, PMDA asked the applicant to include the above guide for dose adjustment in the Precautions for dosage and administration.

The applicant responded that the Precautions for dosage and administration would be described as follows:

Precautions for dosage and administration:

(1) Romiplostim should be used at the minimum dose required therapeutically according to the table below.

Platelet count	Dose adjustment
<50,000/μL	Increase the dose by 1 μg/kg.
50,000/μL to 200,000/μL	Consider decreasing the dose to the minimum level required therapeutically to reduce the risk of haemorrhage.
200,000/μL to 400,000/μL	Decrease the dose by 1 μg/kg.
>400,000/μL	Suspend the administration. Resume the administration in principle at the dose decreased by 1 μg/kg from that before discontinuation if the platelet count has decreased to ≤200,000/μL after discontinuation.

PMDA accepted the applicant's response.

(3) Discontinuation criteria for non-responders to romiplostim

The applicant proposed to provide a caution: when the platelet count does not increase to the level at which the clinically significant haemorrhage risk can be avoided even after 4 consecutive weekly administration at the maximum dose of 10 μg/kg, appropriate measures such as treatment discontinuation should be taken, and the appropriateness of the proposed caution was discussed. The following comments were raised from expert advisors: a period of 4 weeks is needed to determine whether the patient is a responder to romiplostim or not; treatment discontinuation should be considered in a patient in whom the platelet count does not exceed 50,000/μL even after 4 consecutive weekly administration at the dose of 10 μg/kg in consideration that a clinically

significant haemorrhage risk can be avoided in general at a platelet count of 50,000/μL; the treatment may be discontinued if no response is observed after 2 consecutive weekly administration since the platelet count reached the maximum approximately 2 weeks after the single dose of romiplostim in a phase I study; romiplostim may have to be administered at the maximum dose for > 4 weeks if any clinical significance is found in the platelet count maintained by romiplostim even if it may not be high enough to avoid haemorrhage risk because it is difficult to set the criteria for non-responders in consideration that the therapeutic options are limited for second-line and subsequent therapies; it is difficult to set the uniform criteria because the level of platelet count to avoid haemorrhage risk differs from patient to patient, and even the platelet count <50,000/μL provides benefits to some patients.

Taking the above discussions into account, PMDA considers it difficult to set the discontinuation criteria uniformly, but it is necessary to prevent romiplostim from being used carelessly without the effect, as the risk associated with the long-term treatment with romiplostim has still not been clarified. PMDA considers it acceptable to set the applicant's proposal as a guide for discontinuation of romiplostim at present, but it is important to collect the relevant information via post-marketing surveillance. If any new finding is available, appropriate actions should be taken.

(4) Platelet count measurement after discontinuation of romiplostim

PMDA has concluded that the following explanation by the applicant is appropriate: it will be cautioned that, after discontinuation of romiplostim, attention should be paid to a rebound of the platelet count because the platelet count decreases again after the discontinuation, and the platelet count should be measured weekly at least for the first 2 weeks after discontinuation; and it will be cautioned that attention should be paid to haemorrhage after the discontinuation. Concerning the above conclusion of PMDA, the following comments were raised from expert advisors: the platelet count must be monitored after discontinuation of romiplostim as it will obviously decrease because romiplostim is not a drug that radically cures of chronic ITP even though it is difficult to differenciate between a rebound after discontinuation and a change in baseline platelet count; the platelet count should be carefully monitored especially during a period after discontinuation in which the platelet count definitely decreases as rapid changes of the platelet count may increase the haemorrhage risk,. Taking account of the above discussions and settings for similar drugs, PMDA has concluded that the following cautions should be provided: discontinuation of the product may worsen thrombocytopenia; when the product is discontinued, the complete blood count test (erythrocytes, leukocytes, and platelets) should be performed frequently for approximately 4 weeks after that.

(5) Measurement interval of platelet count during romiplostim treatment

PMDA has concluded that the platelet count should be monitored for the safety to be generally ensured in the following manner after the treatment is started at the dose of 1 μg/kg in chronic ITP patients with a platelet count <50,000/μL although the monitoring frequency should be determined on an individual basis: once weekly until the platelet count is stabilized at the maintenance dose; and then at least once every 4 weeks. Concerning the conclusion of PMDA, the following comments were raised from expert advisors: although the above setting is acceptable only as a guide, it is obvious that the platelet count over time is largely different from patient to patient; therefore, it is important that the dose will be adjusted under the supervision and judgment of physicians with adequate knowledge and experience in ITP therapy. Taking the above discussions into account, PMDA has concluded that in addition to the above guide for monitoring frequency, the following caution should be provided: the product should be used under control of physicians with adequate experience in treatment for blood dyscrasia."

3. Other precautions

Non-clinical study data suggested that contribution of renal excretion was increased at the high dose of romiplostim, and serum romiplostim concentrations were increased in patients with renal impairment. According to the information about similar drugs, the risk of thrombosis possibly increases in patients with hepatic impairment. Based on the above, PMDA has concluded that the following actions are appropriate: caution should be provided that the efficacy and safety of romiplostim in patients with renal or hepatic impairment remain unknown due to extremely limited experience with the treatment of such patients in clinical studies; and the post-marketing safety information in such patients should be collected. These conclusions of PMDA were supported by the expert advisors.

Taking the above discussions into account, PMDA has concluded that the patients with renal impairment and those with hepatic impairment should be listed in the Careful Administration section.

Expert advisors pointed out that romiplostim might be administered to patients other than adults with chronic ITP (pediatric patients with ITP, patients with myelodysplastic syndrome or HIV associated thrombocytopenia).

The applicant explained the development status of romiplostim for these diseases as follows:
Amgen Inc. conducted foreign studies in pediatric patients with ITP, myelodysplastic syndrome, or chemotherapy-induced thrombocytopenia. Although the romiplostim development plan in these patients in Japan remains to be determined, based on the medical needs for these diseases and foreign data, the applicant will examine the necessity and feasibility of the development in Japan.

PMDA considers that the development should be implemented without delay in Japan wherever necessary, once the medical needs of romiplostim and appropriateness of the development for diseases other than chronic ITP are confirmed.

Expert advisors presented a concern that romiplostim might worsen the local injury at the subcutaneous injection site as contusion frequently occurred as an adverse event in the clinical studies. In response to this comment, PMDA asked the applicant to explain their view.

The applicant responded as follows:
Of 24 subjects who received romiplostim in the Foreign study 20000137A, 12 subjects experienced contusion (59 events) and 2 subjects experienced injection site contusion (2 events). When the incidence was compared by period, contusion occurred in 9 subjects (21 events) and 10 subjects (38 events) during the treatment period (Days 1 to 23) and observation period (Day 24 and thereafter), respectively; it occurred more frequently during the observation period than the treatment period. Contusion extensively occurred, but the causal relationship to romiplostim was ruled out for all the events. On the other hand, the causal relationship to romiplostim could not be ruled out for injection site contusion, but it was all mild and not associated with skin injury, and the possibility of romiplostim worsening contusion was unknown. Furthermore, in the safety evaluation of romiplostim in the Phase 3 ITP Long-Term Safety Set, the following haemorrhage-related adverse events at the injection site were confirmed. These included infusion site haematoma only in the romiplostim group (1 event, 0.3/100 patient-years), injection site haematoma in both romiplostim (24 events, 7.8/100 patient-years) and untreated group (6 events, 27.3/100 patient-years), and injection site haemorrhage in both romiplostim (3 events, 1.0/100 patient-years) and untreated group (1 event, 4.5/100 patient-years). Although the number of occurrences of haemorrhage-related adverse events at the injection site tended to increase with the decreasing platelet count, the incidences were all low. Accordingly, the applicant determined

that it would not be necessary to provide any cautions for occurrence or worsening of skin injury following romiplostim treatment.

PMDA accepted the applicant's response.

Expert advisors commented that to ensure that the test for neutralizing antibody can be performed immediately upon request from healthcare providers in clinical settings, the testing system should be established and maintained for an extended period. PMDA asked the applicant to explain details of the post-marketing testing system, procedures for handling the request from healthcare providers, and maintenance of the testing system.

The applicant responded as follows:
At present, the post-marketing system for neutralizing antibody measurement is as follows. As done in the Japanese clinical studies, the test is planned to be outsourced to Amgen Inc. to ensure the implementation. (a) Kyowa Hakko Kirin Co., Ltd. accepts a request for antibody test from a medical institution; (b) the company outsources the antibody test to Amgen Inc; (c) after receiving the test results from Amgen Inc. a medical representative of the company reports them to the medical institution. A contract distribution company will collect the specimens from medical institutions and send them to Amgen Inc.

The applicant will make efforts to maintain the post-marketing testing system and to review the test contents and procedures wherever necessary so that responses can be made upon request from healthcare providers in clinical settings.

PMDA accepted the applicant's response.

4. Post-marketing surveillance

The applicant explained details of the post-marketing surveillance as follows:
Post-marketing surveillance will be implemented to confirm the safety and efficacy of long-term treatment with romiplostim (observation period, 1 year) in clinical settings in all patients who start romiplostim treatment within 2 years after market launch of romiplostim. Primary investigation items are set as worsening of thrombocytopenia and haemorrhage-related events after discontinuation of the product; and adverse drug reactions classified into the Blood and lymphatic system disorders (including thrombocytosis, thrombosis/thromboembolism, haemorrhage). Approximately 800 patients are expected to provide relevant medical information within 2 years after the market launch. In response to the applicant's proposal, PMDA concluded that information about the safety and efficacy of long-term treatment with romiplostim should be collected for >1 year, although the applicant's proposal of all patient surveillance plan and primary investigation items are considered largely appropriate. The PMDA's conclusion was supported by the expert advisors. The following comments were raised from expert advisors: it is necessary to ensure that the safety information are collected especially from the patients who will be able to provide the relevant information on the long-term treatment over several years even if all of such patients cannot be followed; as haemorrhage trends might intensify when the platelet count decreases after discontinuation, data on the platelet count as well as adverse events including any haemorrhage trend and subsequent remedies should be collected during an appropriate period after discontinuation; concerning the patient background, the information may be collected only on the selected important items such as medical history, comorbidity, and previous treatment history to prevent the surveillance from requiring complicated procedures.

Taking the above discussions into account, PMDA instructed the applicant to extend the surveillance period, to set the observation period in each patient at 1 year after the treatment start of the product (up to 2 years), and if possible, at 2 years from the patients included in an early phase of the surveillance, and to plan a surveillance in patients treated with the product for >2

years where necessary in consideration of the information and knowledge about the product accumulated in the future such as information collected via post-marketing surveillance and those from foreign studies. In addition, PMDA asked the applicant to consider a post-marketing surveillance plan to collect the following information: development of hematopoietic diseases such as increased bone marrow reticulin or myelofibrosis, MDS in patients treated with the product for an extended period and relevant test results, safety in patients who are consequently found inappropriate for the product; safety and efficacy in patients with renal impairment and those with hepatic impairment; and the relationship between the treatment status of the product (dose, dosing interval), platelet count, and adverse events (at least 1 month after discontinuation if applicable).

The applicant responded as follows:
Patients to be included in the surveillance will be set as all patients who started the product within 5 years after the market launch, and the observation period for each patient will be changed to 2 years and the surveillance period 8 years. The above information indicated by PMDA will be collected. In consideration of the approval status of similar drugs with the same indication, approximately 700 patients are expected to provide relevant medical information within 5 years after the market launch.

PMDA accepted the applicant's response, considering the outline of the proposed post-marketing surveillance protocol submitted by the applicant to be largely appropriate, although the details of the protocol etc., will have to be further examined.

III. Overall Evaluation

As a result of the above review, PMDA concluded that the product may be approved after modifying the indications and the dosage and administration as shown below, with the following conditions. The appropriate re-examination period of the product is 10 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indication]	Chronic idiopathic thrombocytopenic purpura
[Dosage and administration]	The usual initial adult dosage is 1 μg/kg of Romiplostim (Genetical Recombination) administered subcutaneously. After starting the treatment, it should be administered once weekly subcutaneously at the dose depending on the patient's platelet count and other symptoms. The maximum dose is 10 μg/kg once weekly.
[Conditions for approval]	Since the product has only been studied in a limited number of patients in Japan, the applicant is required to conduct a post-marketing drug use-results survey of all the patients treated until data from a certain number of patients have been accumulated in order to understand the background information of patients treated with the product. At the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.