**Report on the Deliberation Results**

June 3, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health 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** | July 31, 2018 |

**Results of Deliberation**

In its meeting held on May 28, 2019, the First Committee on New Drugs concluded that the partial change application for 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 re-examination period is 5 years and 10 months.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. 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 characteristics of patients treated with the product. At the same time, the applicant is required to collect safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

**Japanese Accepted Name (modified INN)*

**Review Report**

May 15, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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|---|---|
| **Brand Name** | Romiplate for S.C. Injection 250 μg |
| **Non-proprietary Name** | Romiplostim (Genetical Recombination) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 31, 2018 |
| **Dosage Form/Strength** | Lyophilized powder for solution for subcutaneous injection: Each vial contains 375 μg of Romiplostim (Genetical Recombination). |
| **Application Classification** | Prescription drug (4) Drug with a new indication, (6) Drug with a new dosage |
| **Items Warranting Special Mention** | None |
| **Reviewing Office** | Office of New Drug I |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product is expected to have efficacy in the treatment of aplastic anemia in patients who have not responded sufficiently to conventional treatments, and that the product has acceptable safety in view of its benefits (see Attachment). The safety and efficacy of the product need to be further investigated via post-marketing surveillance in all patients with aplastic anemia who have not responded sufficiently to conventional treatments and have received the product.

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following conditions.

**Indications**

Chronic idiopathic thrombocytopenic purpura
Aplastic anemia that has not responded sufficiently to conventional treatments

(Underline denotes additions.)

**Dosage and Administration**

Chronic idiopathic thrombocytopenic purpura

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.

Aplastic anemia that has not responded sufficiently to conventional treatments

The usual initial adult dosage is 10 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 condition. The maximum dose is 20 μg/kg once weekly.

(Underline denotes additions.)

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. 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 characteristics of patients treated with the product. At the same time, the applicant is required to collect safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

**Attachment**

**Review Report (1)**

April 26, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

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|---|---|
| **Brand Name** | Romiplate for S.C. Injection 250 μg |
| **Non-proprietary Name** | Romiplostim (Genetical Recombination) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 31, 2018 |
| **Dosage Form/Strength** | Lyophilized powder for solution for subcutaneous injection: Each vial contains 375 μg of Romiplostim (Genetical Recombination). |
| **Proposed Indications** | Chronic idiopathic thrombocytopenic purpura<br>Aplastic anemia<br>(Underline denotes addition.) |

**Proposed Dosage and Administration**

Chronic idiopathic thrombocytopenic purpura

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.

Aplastic anemia

The usual initial adult dosage is 10 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 20 μg/kg once weekly.

(Underline denotes additions.)

**Table of Contents**



**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Aplastic anemia (AA) is designated as a designated intractable disease by the Ministry of Health, Labour and Welfare (MHLW Ministerial Announcement No. 60, dated January 1, 2015) and is one of the bone marrow failure syndromes characterized by pancytopenia in peripheral blood and bone marrow hypoplasia. The concerned disease is associated with anemia symptoms such as shortness of breath on exertion, palpitations, and dizziness, haemorrhage symptoms such as bleeding spot subcutaneous, gingival bleeding, and epistaxis as well as infections.

Treatment of AA is determined by age, severity, availability of a donor, responsiveness to immunosuppressive therapy, etc. A clinical practice guideline in Japan specifies bone marrow transplantation as the first-line therapy for patients with AA who are <40 years old and have a human leukocyte antigen (HLA)-matched sibling donor, but recommends immunosuppressive therapy to patients who are ≥40 years and do not have such donor (Reference Guideline for Clinical Practice on Aplastic Anemia, revised version 2018 [Research Group for Idiopathic Hematopoietic Disorder, the Policy Research Project for Intractable Diseases funded by the Health, Labour and Welfare Sciences Research Grants] "Reference Guideline for Clinical Practice on AA 2018"). As the immunosuppressive therapy, anti-human thymocyte globulin (ATG)/ciclosporin A (CsA) (ATG/CsA) is used, and where necessary, eltrombopag olamine (EPAG) is added. If a response to the initial immunosuppressive therapy is not sufficient, re-administration of ATG/CsA or addition of EPAG (if not used in the initial therapy) may be selected, but it is recognized that the re-administration of ATG/CsA to patients who have not responded sufficiently to the immunosuppressive therapy tends to be poorly effective in the treatment.

Romiplostim (Genetical Recombination) (hereinafter referred to as romiplostim) is a fusion protein composed of peptide chain containing thrombopoietin (TPO) receptor binding domain and human immunoglobulin G1 (IgG1) Fc domain and activates the TPO receptor as with EPAG. In Japan, romiplostim was approved for the indication of "chronic idiopathic thrombocytopenic purpura" in November 2011, and activation of the TPO receptor was suggested to enhance hematopoiesis in multiple lineages *(J Clin Invest.* 1995;96:1683-7, *J Leukoc Biol.* 2000;68:137-43, etc.). On the basis of such background, development of romiplostim for an indication of aplastic anemia was initiated.

The applicant has filed a partial change application as a global phase II/III study has demonstrated the efficacy and safety of romiplostim in patients with AA who did not respond sufficiently to conventional treatments.

As of March 2019, romiplostim is approved in ≥60 countries including the US and European countries, but the indication of aplastic anemia has not been approved in any country or region.

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is for a new indication and a new dosage, no data relating to quality of romiplostim were submitted.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is for a new indication and a new dosage, no new study data were submitted owing to unavailability of a disease model animal appropriate for evaluating a pharmacological effect of romiplostim on AA. Romiplostim activates the TPO receptor as an agonist, and activation of the TPO receptor was suggested to enhance hematopoiesis in multiple lineages (*J Clin Invest.* 1995;96:1683-7, *J Leukoc Biol.* 2000;68:137-43, etc.), based on which romiplostim is expected to facilitate proliferation of blood cells in multiple lineages.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is for a new indication and a new dosage, no new data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of romiplostim had been evaluated at the initial regulatory review (Review Report of "Romiplate for S.C. Injection 250 μg" on November 17, 2010).

## 5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for a new indication and a new dosage, no data on non-clinical toxicity of romiplostim were submitted.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum romiplostim concentrations were determined by a validated method based on enzyme linked immunosorbent assay (ELISA), and the lower limit of quantification was 15 pg/mL. Anti-romiplostim antibody and anti-TPO antibody in serum were determined by a validated method based on surface plasmon resonance.

### 6.2 Clinical pharmacology

#### 6.2.1 Global phase II/III study (CTD 5.3.5.2-2, Study 531-002 [March 2016 to June 2018, to be continued until approval])

Serum romiplostim concentrations after multiple subcutaneous administration of romiplostim were investigated in Japanese and Korean patients with AA who had not sufficiently responded to conventional treatments.

Romiplostim was administered once weekly subcutaneously at 10 μg/kg for the first 4 weeks of treatment (from Weeks 1 to 4) and then at 5 to 20 μg/kg according to the platelet response and blood count from Weeks 5 to 52.

Table 1 shows pharmacokinetic parameters of romiplostim in serum at Week 4.

**Table 1. Pharmacokinetic parameters of romiplostim in serum at Week 4 in patients with AA who had not sufficiently responded to conventional treatments (global phase II/III study)**

| Dose of romiplostim | Study population | n | $C_{max}$ (pg/mL) | $t_{max}$ (h) | $AUC_{0-t}$ (pg·h/mL) | $t_{1/2}$ (h) |
|---|---|---|---|---|---|---|
| 10 μg/kg | All patients | 13 | 5,040 ± 2,800 | 14.0 ± 11.4 | 267,000 ± 150,000 | 90.0 ± 35.6 |
| | Japanese | 8 | 5,810 ± 3,310 | 16.4 ± 12.7 | 305,000 ± 175,000 | 108.5 ± 32.6 |
| | Koreans | 5 | 3,800 ± 1,150 | 10.1 ± 8.8 | 205,000 ± 81,000 | 60.4 ± 12.8 |

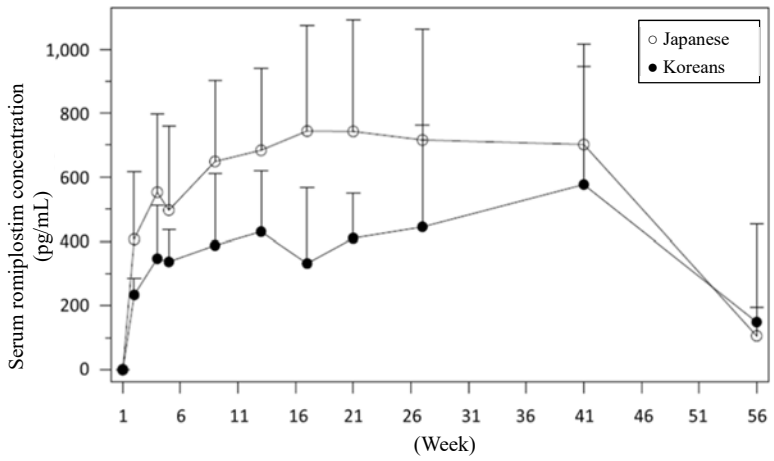
Mean ± standard deviation (SD)

Table 2 shows changes in dose of romiplostim over time. The dose of romiplostim was maintained at a certain level in both Japanese and Korean patients with AA at Week 13 thereafter. Figure 1 shows changes in trough concentrations[1)] of romiplostim in serum. In Korean patients with AA, time required for serum romiplostim concentrations to reach the steady state after the dose of romiplostim was almost maintained at a certain level tended to be longer than that in Japanese patients. At Week 41 of romiplostim treatment, serum romiplostim concentrations in Japanese patients with AA were similar to those in Korean patients.

**Table 2. Changes in dose of romiplostim (μg/kg) (global phase II/III study)**

| Week | 1-4 | 5 | 9 | 13 | 17 | 21 |
|---|---|---|---|---|---|---|
| Japanese | 10.0 | 14.2 ± 1.9 | 16.5 ± 4.3 | 16.9 ± 4.8 | 16.8 ± 5.0 | 16.8 ± 4.5 |
| Koreans | 10.0 | 13.6 ± 2.4 | 15.0 ± 5.0 | 17.1 ± 3.9 | 17.1 ± 3.9 | 16.4 ± 4.8 |
| Week | 24 | 27 | 31 | 35 | 41 | |
| Japanese | 16.4 ± 5.6 | 16.2 ± 5.7 | 16.0 ± 6.2 | 16.0 ± 5.8 | 15.5 ± 5.1 | |
| Koreans | 15.7 ± 6.1 | 15.0 ± 7.6 | 15.7 ± 6.1 | 15.7 ± 6.1 | 14.3 ± 8.4 | |

Mean ± SD




| Week | | 1 | 2 | 4 | 5 | 9 | 13 | 17 | 21 | 27 | 41 | 56[a)] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| n | Japanese | 23 | 8 | 24 | 8 | 22 | 23 | 22 | 22 | 21 | 20 | 24 |
| | Koreans | 7 | 5 | 7 | 5 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

a) In patients who discontinued the romiplostim treatment, serum romiplostim concentrations 4 weeks after the last dose were used.

**Figure 1. Changes in serum romiplostim concentration in Japanese and Korean patients with AA (global phase II/III study)**

Anti-romiplostim antibody and anti-TPO antibody were detected only in 1 Japanese patient with AA each,[2)] but both of them were negative for neutralizing antibodies.

1) Serum romiplostim concentrations in 31 patients (24 Japanese and 7 Koreans)
2) The incidence was 3.2% (1 of 31) of patients in the entire population, 4.2% (1 of 24) of patients in the Japanese population, and 0% (0 of 7) of patients in the Korean population.

## 6.R Outline of the review conducted by PMDA

The applicant's explanation about changes in serum romiplostim concentration in Japanese and Korean patients with AA:

In the global phase II/III study in patients with AA, the dose of romiplostim was maintained at a certain level in both Japanese and Korean patients with AA at Week 13 thereafter. In light of the elimination half-life of romiplostim, the serum romiplostim concentration is theoretically considered to reach the steady state 2 to 3 weeks after the dose titration. In Korean patients with AA, however, time required for serum romiplostim concentrations to reach the steady state after the dose of romiplostim was almost maintained at a certain level tended to be longer than that in Japanese patients (Figure 1). Although the reason for the increasing trend of time required for serum romiplostim concentrations to reach the steady state in Korean patients with AA remains unknown, the difference in pharmacokinetics of romiplostim between Japanese and Korean patients with AA is considered to raise no clinically relevant problems for the following reasons:

- Romiplostim is a fusion protein composed of human IgG1 Fc domain and eliminated mainly through degradation of the protein as with IgG monoclonal antibodies, and thus the pharmacokinetics of romiplostim is considered unlikely to be affected by ethnic differences.

- In the global study, the dose of romiplostim at Week 5 thereafter was titrated every 4 weeks according to the platelet response and blood count. Changes in dose in Japanese patients were similar to those in Korean patients, and the dose was almost maintained at a certain level at Week 13 thereafter (Table 2). The dose necessary for treatment of AA is therefore considered to have been administered to both Japanese and Korean patients.

- For the efficacy, no different trend was observed between the Japanese and Korean populations in "the platelet response rate, erythrocyte response rate, or neutrophil response rate at Week 27" of the global study [see Section 7.R.1.3].

- For the safety, adverse events in the global study presented no trends that might raise a clinically relevant problem in either the Japanese or Korean population [see Section 7.R.2.1].

PMDA considers that the reason for the increasing trend of time required for serum romiplostim concentrations to reach the steady state in Korean patients with AA is unknown. The ethnic difference in pharmacokinetics of romiplostim between Japanese and Korean patients is, however, considered to raise no clinically relevant problems from the following aspects: (1) The dose of romiplostim will be titrated according to the patient's condition; and (2) the global study presented no particularly different trends in the efficacy and safety of romiplostim between the Japanese and Korean patients.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data, in the form of results from the foreign phase II study (Study 531-KR001) and global phase II/III study (Study 531-002) as provided in Table 3.

**Table 3. Outline of evaluation data on efficacy and safety**

| Phase (country) | Study identifier | Study design | Study population | Treatment period | Dose (n) | Primary endpoint |
|---|---|---|---|---|---|---|
| Foreign phase II (Korea) | 531-KR001 | Open-label Parallel-group | Patients with AA who have not sufficiently responded to conventional treatments | 156 weeks | Romiplostim 1 μg/kg (n = 7)<br>Romiplostim 3 μg/kg (n = 9)<br>Romiplostim 6 μg/kg (n = 9)<br>Romiplostim 10 μg/kg (n = 10) | Platelet response rate at Week 9<br>Romiplostim 1 μg/kg, 0%<br>Romiplostim 3 μg/kg, 0%<br>Romiplostim 6 μg/kg, 33.3%<br>Romiplostim 10 μg/kg, 70.0% |
| Global phase II/III (Japan, Korea) | 531-002 | Open-label Uncontrolled | Patients with AA who have not sufficiently responded to conventional treatments | 52 weeks | Romiplostim (n = 31) | Hematological response rate at Week 27<br>83.9% |

Severity classification of AA in the global study provided in Table 4 was established based on Reference Guideline for Clinical Practice on Aplastic Anemia, revised version 2014. The grading criteria for bone marrow reticulin[3)] in the foreign study and the global study provided in Table 5 were established based on *Bone Marrow Pathology* 2nd edition (Blackwell Science Ltd, 2001).

**Table 4. Severity classification of AA (global phase II/III study)**

| Stage | Severity | Criteria |
|---|---|---|
| Stage 1 | Mild | Condition that does not meet any of the criteria below |
| Stage 2 | Moderate | Condition that meets ≥2 items of the criteria provided below<br>Reticulocyte count <60,000/μL, neutrophil count <1,000/μL, platelet count <50,000/μL |
| Stage 3 | Slightly severe | Condition that meets ≥2 items of the criteria provided below and needs periodic red blood cell transfusion<br>Reticulocyte count <60,000/μL, neutrophil count <1,000/μL, platelet count <50,000/μL |
| Stage 4 | Severe | Condition that meets ≥2 items of the criteria provided below<br>Reticulocyte count <20,000/μL, neutrophil count <500/μL, platelet count <20,000/μL |
| Stage 5 | Very severe | Condition that meets the item for neutrophil count <200/μL and ≥1 item of the criteria provided below<br>Reticulocyte count <20,000/μL, platelet count <20,000/μL |

**Table 5. Grading criteria for bone marrow reticulin**

| Grade | Criteria |
|---|---|
| 0 | No reticular fibers |
| 1 | Diffuse reticular fibers and local foci of reticular fibers |
| 2 | Foci of reticular fibers widely spread throughout the specimen |
| 3 | Coarse reticular fibers with no evidence of collagen fibers (trichrome stain negative) |
| 4 | Coarse reticular fibers with evidence of collagen fibers (trichrome stain positive) |

### 7.1 Foreign phase II study (CTD 5.3.5.2-1, Study 531-KR001 [April 2014 to November 2017])

A multi-center, randomized, open-label, parallel-group study was conducted in patients with AA who had not sufficiently responded to conventional treatments (Table 6) (target sample size, 32 patients [8 per group]) to evaluate the efficacy and safety of romiplostim at 2 study centers in Korea.

3) Bone marrow reticulin is a reticular fiber of which an increase is observed in the bone marrow findings at an early stage of myelofibrosis. Chronic stimulation of megakaryocytopoiesis through activation of the TPO receptor may progress reticulin fiber formation and fibrogenesis in the bone marrow. Because increased bone marrow reticulin is a known adverse drug reaction of romiplostim, exclusion criteria for bone marrow reticulin were established from a safety viewpoint.

**Table 6. Major inclusion and exclusion criteria (foreign phase II study)**

| |
|---|
| **Major inclusion criteria**<br>• Patients aged ≥19 years<br>• Patients who have not sufficiently responded to immunosuppressive therapy<br>• Patients who have received at least 1 course of a combination therapy of horse or rabbit-derived ATG with CsA<br>• Patients with platelet count ≤30,000/μL |
| **Major exclusion criteria**<br>• Patients with bone marrow reticulin Grade of ≥2 (Table 5)<br>• Patients with thrombocytopenia attributable to a non-AA pathological condition (MDS, chronic ITP, hepatic cirrhosis, etc.)<br>• Patients with a comorbidity of PNH (serum LDH level >1.5 upper limit of institutional reference range) predominantly manifested as hemolysis<br>• Patients who have received drugs including the following AA treatments within a certain period before the start of study treatment:<br>  • ATG within 6 months<br>  • CsA or anabolic steroid within 6 weeks<br>• Patients who are scheduled to receive hematopoietic stem cell transplantation within 1 year |

Romiplostim was administered subcutaneously once weekly at 1, 3, 6 or 10 μg/kg from Weeks 1 to 8. From Weeks 9 to 52, romiplostim was administered subcutaneously once weekly in accordance with the criteria in Table 7. From Weeks 53 to 156, romiplostim was administered subcutaneously once weekly in accordance with the criteria in Table 7 to patients who had shown a platelet response[4)] in the last 8 weeks (Weeks 46 to 53). Concomitant use of ATG was prohibited.

4) Patients meeting either of the following criteria were assessed to show a platelet response (but patients who received platelet transfusion within 7 days were assessed to show "no response"):
- Platelet count is increased by ≥20,000/μL from baseline.
- Platelet count is ≥10,000/μL and increased by ≥100% from baseline.

**Table 7. Dosage and administration (foreign phase II study)**

| |
|---|
| Dosage and administration from Weeks 1-8 |
| Dosage and administration<br>Romiplostim 1, 3, 6 or 10 μg/kg is administered subcutaneously once weekly for 8 weeks.<br>Dose titration is not allowed except when the platelet count is increased above the reference level.* |
| Dosage and administration from Weeks 9-52 and outline of dose titration method |
| **Dosage and administration**<br>Romiplostim 1-20 μg/kg is administered subcutaneously once weekly for 44 weeks, starting with the dose at Week 8.[a)]<br>**Dose titration method**<br>• The dose is titrated in single steps of 1, 3, 6, 10, 13, 16, and 20 μg/kg.<br>• If no platelet response is observed 4 weeks after a dose increase, the dose is increased by 1 level.[b)] If a platelet response is observed, the dose may be titrated in single steps to maintain the platelet response at the discretion of the investigator.<br>• If the platelet count is increased above the reference level,* the dose is reduced or suspended. If any safety concern is raised, the dose may be reduced at the discretion of the investigator. |
| Dosage and administration from Weeks 53-156 and outline of dose titration method |
| **Dosage and administration**<br>Romiplostim 3-20 μg/kg is administered subcutaneously once weekly for 104 weeks, starting with the dose at Week 52.[c)]<br>**Dose titration method**<br>• The dose is titrated in single steps of 3, 6, 10, 13, 16, and 20 μg/kg.<br>• The dose may be titrated in single steps to maintain the platelet response at the discretion of the investigator.<br>• If a patient has presented the platelet count >50,000/μL, Hb level >10.0 g/dL, and neutrophil count >1,000/μL for 8 consecutive weeks while receiving the same dose and has not received blood transfusion, the dose is reduced by 1 level. If the patient has presented the platelet count >50,000/μL, Hb level >10.0 g/dL, and neutrophil count >1,000/μL for 4 consecutive weeks after dose reduction while receiving the same reduced dose and has not received blood transfusion, the dose is further reduced by 1 level (the dose may be tapered by 1 level every 4 weeks, and if the dose is already 3 μg/kg, the dose is suspended).<br>• If the platelet count is increased above the reference level,* the dose is reduced or suspended. If any safety concern is raised, the dose may be reduced at the discretion of the investigator.<br>• If a patient has presented any of platelet count <30,000/μL, Hb level <9.0 g/dL, or neutrophil count <500/μL while the dose is being tapered, the dose is titrated by 1 level to maintain the platelet response at the discretion of the investigator (if the dose is being suspended, it is resumed at 3 μg/kg). |
| * Measures to be taken if the platelet count is increased above the reference level (applicable throughout the study) |
| • If the platelet count is >200,000/μL, reduce the dose by 1 level.<br>• If the platelet count is >400,000/μL, suspend the dose.<br>If the platelet count is reduced to <200,000/μL after the suspension, resume the treatment at the dose reduced by 1 level from that at the time of suspension, or if the platelet count is reduced to ≤50,000/μL, resume the treatment at the same dose as that at the time of suspension.[d)] |

a) If no platelet response is observed at Week 9, the treatment is started at the dose increased by 1 level.
b) If no platelet response is observed but there is any concern about onset or exacerbation of adverse events, the dose may be kept unchanged at the discretion of the investigator.
c) The dose may be titrated at Week 53, if the investigator considers it necessary.
d) If the dose of romiplostim before suspension is 1 μg/kg (Weeks 1 to 52) or 3 μg/kg (Weeks 53 to 156), the treatment is not resumed even when the platelet count reaches <200,000/μL, and it is resumed at the same dose as that before suspension only when the platelet count reaches ≤50,000/μL.

All of 35 randomized patients (7 in the romiplostim 1 μg/kg group, 9 in the 3 μg/kg group, 9 in the 6 μg/kg group, 10 in the 10 μg/kg group) received romiplostim and were included in the safety analysis set. Of these, 33 patients (7 in the 1 μg/kg group, 7 in the 3 μg/kg group, 9 in the 6 μg/kg group, 10 in the 10 μg/kg group) were included in the per protocol set (PPS) and the major efficacy analysis set, excluding 2 patients who discontinued the study because of "being found ineligible" (1 in the 3 μg/kg group) and "infeasibility of laboratory test or observation" (1 in the 3 μg/kg group). Discontinuation occurred in 1 patient (3 μg/kg group) between Weeks 1 and 8, 16 patients (3 in the 1 μg/kg group, 5 in the 3 μg/kg group, 4 each in the 6 μg/kg group and 10 μg/kg group) between Weeks 9 and 52, and 8 patients (2 each in the 1 μg/kg group and 3 μg/kg group, 1 in the 6 μg/kg group, 3 in the 10 μg/kg group) between Weeks 53 and 156. Reasons for the discontinuation included "insufficient response" in 15 patients (4 each in the 1 μg/kg group, 3 μg/kg group, and 6 μg/kg group, 3 in the 10 μg/kg group), "consent withdrawal" in 7 patients (1 in the 1 μg/kg group, 2 in the 3 μg/kg group, 1 in the 6 μg/kg group, 3 in the 10 μg/kg group), "being found ineligible" in 1 patient (3 μg/kg group), "infeasibility of

laboratory test or observation" in 1 patient (3 μg/kg group), and "adverse events" in 1 patient (10 μg/kg group).

For the efficacy, the platelet response rate at Week 9 (percentage of patients who were assessed to show a platelet response[4)]) [95% confidence interval (CI)], the primary endpoint, was 0% (0 of 7) of patients in the romiplostim 1 μg/kg group [0.0, 41.0], 0% (0 of 7) of patients in the 3 μg/kg group [0.0, 41.0], 33.3% (3 of 9) of patients in the 6 μg/kg group [7.5, 70.1], and 70.0% (7 of 10) of patients in the 10 μg/kg group [34.8, 93.3].

For the safety, adverse events occurred in 42.9% (3 of 7) of patients in the romiplostim 1 μg/kg group, 55.6% (5 of 9) of patients in the 3 μg/kg group, 77.8% (7 of 9) of patients in the 6 μg/kg group, and 40.0% (4 of 10) of patients in the 10 μg/kg group between Weeks 1 and 8. Adverse events reported by ≥2 patients in any group were fatigue (2 of 9 patients [22.2%] in the 3 μg/kg group, 3 of 9 patients [33.3%] in the 6 μg/kg group), myalgia (1 of 7 patients [14.3%] in the 1 μg/kg group, 2 of 9 patients [22.2%] in the 3 μg/kg group, 2 of 9 patients [22.2%] in the 6 μg/kg group), transfusion reaction (2 of 7 patients [28.6%] in the 1 μg/kg group, 1 of 10 patients [10.0%] in the 10 μg/kg group), and insomnia (2 of 9 patients [22.2%] in the 6 μg/kg group). Adverse drug reactions occurred in 22.2% (2 of 9) of patients in the 3 μg/kg group (fatigue and myalgia, and myalgia in 1 patient each) and 11.1% (1 of 9) of patients in the 6 μg/kg group (fatigue, myalgia, and dizziness), but no adverse drug reaction occurred in the 1 μg/kg group or 10 μg/kg group.

During the entire study period (from Weeks 1 to 156), adverse events occurred in 100% (7 of 7) of patients in the romiplostim 1 μg/kg group, 77.8% (7 of 9) of patients in the 3 μg/kg group, 100% (9 of 9) of patients in the 6 μg/kg group, and 90.0% (9 of 10) of patients in the 10 μg/kg group. Table 8 shows adverse events reported by ≥2 patients in any group. Adverse drug reactions occurred in 22.2% (2 of 9) of patients in the 3 μg/kg group (fatigue and myalgia, and myalgia in 1 patient each) and 11.1% (1 of 9) of patients in the 6 μg/kg group (fatigue, myalgia, and dizziness), but no adverse drug reaction occurred in the 1 μg/kg group or 10 μg/kg group.

**Table 8. Adverse events reported by ≥2 patients in any group (foreign phase II study, entire period [from Weeks 1-156])**

| | Romiplostim | | | | Overall (n = 35) |
|---|---|---|---|---|---|
| | 1 μg/kg (n = 7) | 3 μg/kg (n = 9) | 6 μg/kg (n = 9) | 10 μg/kg (n = 10) | |
| All adverse events | 100 (7) | 77.8 (7) | 100 (9) | 90.0 (9) | 91.4 (32) |
| Upper respiratory tract infection | 71.4 (5) | 33.3 (3) | 33.3 (3) | 50.0 (5) | 45.7 (16) |
| Fatigue | 14.3 (1) | 22.2 (2) | 33.3 (3) | 20.0 (2) | 22.9 (8) |
| Transfusion reaction | 42.9 (3) | 0 (0) | 11.1 (1) | 30.0 (3) | 20.0 (7) |
| Myalgia | 14.3 (1) | 33.3 (3) | 22.2 (2) | 0 (0) | 17.1 (6) |
| Dyspepsia | 0 (0) | 22.2 (2) | 22.2 (2) | 0 (0) | 11.4 (4) |
| Urticaria | 0 (0) | 22.2 (2) | 22.2 (2) | 0 (0) | 11.4 (4) |
| Abdominal pain upper | 0 (0) | 0 (0) | 22.2 (2) | 10.0 (1) | 8.6 (3) |
| Dizziness | 0 (0) | 11.1 (1) | 22.2 (2) | 0 (0) | 8.6 (3) |
| Insomnia | 14.3 (1) | 0 (0) | 22.2 (2) | 0 (0) | 8.6 (3) |
| Mouth haemorrhage | 0 (0) | 22.2 (2) | 11.1 (1) | 0 (0) | 8.6 (3) |
| Purpura | 0 (0) | 22.2 (2) | 11.1 (1) | 0 (0) | 8.6 (3) |
| Cystitis | 0 (0) | 0 (0) | 22.2 (2) | 0 (0) | 5.7 (2) |
| Pruritus | 0 (0) | 0 (0) | 22.2 (2) | 0 (0) | 5.7 (2) |
| Rash | 0 (0) | 0 (0) | 22.2 (2) | 0 (0) | 5.7 (2) |

Medical Dictionary for Regulatory Activities (MedDRA) ver. 20.1. Incidence (%) (number of patients with the event)

Death occurred in 1 patient in the romiplostim 3 μg/kg group (sepsis[5)]), but a causal relationship to romiplostim was denied. Serious adverse events other than death occurred in 22.2% (2 of 9) of patients in the 3 μg/kg group (febrile neutropenia and cellulitis in 1 patient each), 22.2% (2 of 9) of patients in the 6 μg/kg group (appendicitis, and tendon injury and macular fibrosis in 1 patient each), and 30.0% (3 of 10) of patients in the 10 μg/kg group (cataract and retinal detachment, inguinal hernia, and transfusion reaction in 1 patient each), but no serious adverse events occurred in the 1 μg/kg group. A causal relationship to romiplostim was denied for all events. An adverse event leading to treatment discontinuation occurred in 10.0% (1 of 10) of patients in the romiplostim 10 μg group (transfusion reaction), but a causal relationship to romiplostim was denied.

During the entire study period (from Weeks 1 to 156) of the foreign phase II study, no substantial differences were observed in the incidence of adverse events or adverse drug reactions between the groups, and there were no events that would raise a particular problem.

### 7.2 Global phase II/III study (CTD 5.3.5.2-2, Study 531-002 [March 2016 to June 2018, to be continued until approval])

A multi-center, open-label, uncontrolled study was conducted in patients with AA who had not sufficiently responded to conventional treatments (Table 9) (target sample size, 27 patients [20 Japanese, 7 Koreans]) to evaluate the efficacy and safety of romiplostim at 16 study centers in Japan and 2 study centers in Korea. Table 10 shows the criteria for response assessment used in this study. In addition, concomitant use of ATG was prohibited.

5) Female aged 58 years (3 μg/kg group). Febrile neutropenia occurred on Day 7 of romiplostim treatment but resolved on Day 10. Sepsis occurred on Day 26, and she was withdrawn from the trial on Day 64. Death was confirmed based on information from her family on Day 71 (date of death unknown). A causal relationship to romiplostim was denied for both sepsis and febrile neutropenia.

**Table 9. Major inclusion and exclusion criteria (global phase II/III study)**

| |
|---|
| **Major inclusion criteria**<br>• Japanese patients aged ≥20 years or Korean patients aged ≥19 years<br>• Patients who have not sufficiently responded to immunosuppressive therapies that include horse or rabbit-derived ATG or who have not sufficiently responded to CsA and are not eligible for ATG<br>• Patients with platelet count ≤30,000/μL |
| **Major exclusion criteria**<br>• Patients with bone marrow reticulin Grade of ≥2 (Table 5)<br>• Patients in whom blast cells account for >2% of cells in the bone marrow<br>• Patients with thrombocytopenia attributable to a non-AA pathological condition (MDS, chronic ITP, hepatic cirrhosis, etc.)<br>• Patients with a comorbidity of PNH (serum LDH level >1.5 upper limit of institutional reference range) predominantly manifested as hemolysis<br>• Patients who have received drugs including the followings AA treatments before the start of study treatment:<br>  • ATG within 6 months<br>  • CsA or anabolic steroid within 6 weeks (patients may be enrolled if they have received CsA or anabolic steroid for ≥6 months with stable blood counts and are to continue receiving treatments throughout the study at the same dose as that at 6 weeks before the start of the study treatment)<br>• Patients who are scheduled to receive hematopoietic stem cell transplantation within 1 year<br>• Patients in whom abnormality is found in chromosome banding of bone marrow cells |

**Table 10. Criteria for response assessment (global phase II/III study)**

| Endpoint | Definition |
|---|---|
| Hematological response | Any of the following criteria for platelet response, erythrocyte response or neutrophil response is met. |
| Platelet response | Any of the following criteria is met:<br>• Platelet count is increased by ≥20,000/μL from baseline.<br>• Platelet count is ≥10,000/μL and increased by ≥100% from baseline.<br>• In a patient who received platelet transfusion within 8 weeks before start of the treatment, no platelet transfusion has been performed for 8 consecutive weeks. |
| Erythrocyte response | Any of the following criteria is met:<br>• In a patient with the baseline Hb level <9.0 g/dL, the Hb level is increased by ≥1.5 g/dL without red blood cell transfusion.<br>• In a patient who received red blood cell transfusion within 8 weeks before start of the treatment, the volume of red blood cell transfusion during a treatment period of 8 consecutive weeks is decreased by ≥800 mL from that during a pre-dose period of 8 weeks. |
| Neutrophil response | Any of the following criteria is met:<br>• In a patient with the baseline neutrophil count <500/μL, the neutrophil count is increased by ≥100% from the baseline count.<br>• In a patient with the baseline neutrophil count <1,000/μL, the neutrophil count is increased by ≥500/μL from the baseline count. |

Based on Table 11, romiplostim was administered subcutaneously once weekly for 52 weeks.

**Table 11. Dosage and administration (global phase II/III study)**

| Dosage and administration |
|---|
| Romiplostim is administered subcutaneously once weekly for 52 weeks with a starting dose of 10 μg/kg.<br>The dose is fixed until Week 4 and is titrated according to the dose titration method at Week 5 thereafter. |
| Outline of dose titration method |
| • The dose is titrated in single steps of 5, 10, 15, and 20 μg/kg.<br>• If a platelet response is not observed at 1 timepoint during 4 consecutive weeks, the dose is increased by 1 level every 4 weeks.[a)]<br>• If a patient has presented the platelet count >50,000/μL, Hb level >10.0 g/dL, and neutrophil count >1,000/μL for 8 consecutive weeks while receiving the same dose and has not received blood transfusion, the dose is reduced by 1 level. If a patient has presented the platelet count >50,000/μL, Hb level >10.0 g/dL, and neutrophil count >1,000/μL for 4 consecutive weeks after dose reduction while receiving the same reduced dose and has not received blood transfusion, the dose is further reduced by 1 level (the dose may be tapered by 1 level every 4 weeks, and if the dose is already 5 μg/kg, the dose is suspended).<br>• If the platelet count is increased above the reference level, the dose is reduced or suspended as described below.<br>  • If the platelet count is >200,000/μL, reduce the dose by 1 level.<br>  • If the platelet count is >400,000/μL, suspend the dose. If the platelet count is reduced to <200,000/μL after the suspension, resume the treatment at the dose reduced by 1 level from that at the time of suspension, or if the platelet count is reduced to ≤50,000/μL, resume the treatment at the same dose as that at the time of suspension.[b)]<br>• If any safety concern is raised, the treatment may be suspended[c)] or the dose may be reduced in single steps at the discretion of the investigator.<br>• If a patient has presented any of platelet count <30,000 /μL, Hb level <9.0 g/dL, or neutrophil count <500/μL while the dose is being tapered, the dose is increased by 1 level (if the dose is being suspended, it is resumed at 5 μg/kg). |

a) If no platelet response is observed but there is any concern about onset or exacerbation of adverse events, the dose may be kept unchanged at the discretion of the investigator or sub-investigator. If a platelet response is observed, the dose may be increased in single steps every 4 weeks when justified by the investigator or sub-investigator.

b) If the dose of romiplostim at the time of suspension is 5 μg/kg, the treatment is not resumed even when the platelet count reaches <200,000/μL, and the treatment is resumed at the same dose as that at the time of suspension only when the platelet count reaches ≤50,000/μL.

c) If the romiplostim treatment is resumed after suspension, the dose is reduced by 1 level from that at the time of suspension (if the dose at the time of suspension is 5 μg/kg, the treatment is resumed at the same dose).

All of 31 patients included in the study (24 Japanese, 7 Koreans) received romiplostim and were included in the full analysis set (FAS) and safety analysis set, and the FAS was used as the major efficacy analysis set. Discontinuation occurred in 4 patients owing to "insufficient response" for all of these.

For the efficacy, the hematological response rate at Week 27 (percentage of patients who met the criteria for response assessment in Table 10) [95% CI], the primary endpoint, was 83.9% (26 of 31 patients) [66.3, 94.5], and the lower limit of the 95% CI exceeded 15%, the pre-determined threshold (Table 12).

**Table 12. Hematological response rate at Week 27 (global phase II/III study, FAS)**

| | Japanese subpopulation (n = 24) | Korean subpopulation (n = 7) | Overall populations (n = 31) |
|---|---|---|---|
| Hematological response rate | 79.2 (19) [57.8, 92.9] | 100 (7) [59.0, 100] | 83.9 (26) [66.3, 94.5] |

Response rate (%) (number of responders) [95% CI]. Patients who discontinued the study or patients with missing values were handled as non-responders.

For the safety, adverse events occurred in 93.5% (29 of 31) of patients, and adverse drug reactions occurred in 54.8% (17 of 31) of patients during the treatment period up to Week 53. Tables 13 and 14 show adverse events and adverse drug reactions reported by ≥2 patients, respectively.

**Table 13. Adverse events reported by ≥2 patients (global phase II/III study [up to Week 53])**

| | Romiplostim (n = 31) | | Romiplostim (n = 31) |
|---|---|---|---|
| All adverse events | 93.5 (29) | Oropharyngeal pain | 9.7 (3) |
| Nasopharyngitis | 41.9 (13) | Chills | 6.5 (2) |
| Upper respiratory tract infection | 25.8 (8) | Cystitis | 6.5 (2) |
| Pyrexia | 19.4 (6) | Herpes zoster | 6.5 (2) |
| Headache | 16.1 (5) | Periodontitis | 6.5 (2) |
| Diarrhoea | 12.9 (4) | Pharyngitis | 6.5 (2) |
| Muscle spasms | 12.9 (4) | Allergic transfusion reaction | 6.5 (2) |
| Abdominal pain upper | 9.7 (3) | AST increased | 6.5 (2) |
| Malaise | 9.7 (3) | Fibrin D dimer increased | 6.5 (2) |
| Influenza | 9.7 (3) | Hyperuricaemia | 6.5 (2) |
| Contusion | 9.7 (3) | Renal impairment | 6.5 (2) |
| ALT increased | 9.7 (3) | Rash | 6.5 (2) |
| Back pain | 9.7 (3) | Urticaria | 6.5 (2) |
| Pain in extremity | 9.7 (3) | | |

MedDRA ver. 20.1. Incidence (%) (number of patients with the event)

**Table 14. Adverse drug reactions reported by ≥2 patients (global phase II/III study [up to Week 53])**

| | Romiplostim (n = 31) | | Romiplostim (n = 31) |
|---|---|---|---|
| All adverse drug reactions | 54.8 (17) | ALT increased | 6.5 (2) |
| Headache | 12.9 (4) | Fibrin D dimer increased | 6.5 (2) |
| Muscle spasms | 12.9 (4) | Pain in extremity | 6.5 (2) |
| Malaise | 6.5 (2) | | |

MedDRA ver. 20.1. Incidence (%) (number of patients with the event)

No deaths occurred. Serious adverse events occurred in 6.5% (2 of 31) of patients (sepsis and spondylitis in 1 patient each), but a causal relationship to romiplostim was denied for either event. No adverse events leading to treatment discontinuation occurred.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

Based on the review in Sections 7.R.1.1 to 7.R.1.4 below, PMDA considers that romiplostim is expected to have the efficacy in the treatment of patients with AA who has not sufficiently responded to conventional treatments.

#### 7.R.1.1 Study design of phase II/III study

The applicant's explanation about justification of the study design of the phase II/III study in patients with AA who did not sufficiently responded to conventional treatments:

In Japan, the number of patients with AA is estimated to be approximately 14,000 as of 2013 (FY2014 General Partial Research Report, Research for Idiopathic Hematopoietic Disorder, the Policy Research Project for Intractable Diseases funded by the Health, Labour and Welfare Sciences Research Grants). Of these, patients who do not sufficiently respond to conventional treatments, patients eligible for romiplostim, are further limited. There are no large differences in diagnosis of AA or the treatment method between Japan and Korea, and the study was conducted as a global study in Japan and Korea. Still, the number of patients eligible for the global study was too small to establish a control group, and thus the study was conducted in an open-label, uncontrolled manner.

PMDA has accepted that the phase II/III study was conducted as the open-label, uncontrolled global study because the number of patients with AA who do not sufficiently respond to conventional treatments is limited.

### 7.R.1.2 Primary endpoint

The applicant's explanation about rationales for establishment of the primary endpoint in the global phase II/III study and results:

AA is a bone marrow failure syndrome characterized by pancytopenia. If romiplostim improves any of the platelet count, hemoglobin (Hb) level, or neutrophil count in patients with AA, reduction of a risk of haemorrhage or severe infection and weaning from platelet transfusion or red blood cell transfusion can be expected. Use of romiplostim was therefore considered to have a clinical significance. In the concerned global study, accordingly, the primary endpoint was established as the percentage of patients who showed a "hematological response" representative of an improved condition in any of 3 blood cell lineages (platelet, erythrocyte, and neutrophil) (patients who met the criteria for response assessment in Table 10). For the evaluation timing of the primary endpoint, the treatment should be continued for at least 6 months to evaluate the efficacy of romiplostim because the treatment of AA generally requires an extended period. In addition, taking into account that the percentage of patients presenting a response to romiplostim was increased with the treatment period but levelled off at Week 24 in the 10 μg/kg group in the foreign phase II study; and a response to immunosuppressive therapy (ATG) was assessed at Month 6 ("Review Report of Thymoglobulin for Intravenous Infusions 25 mg" [dated May 15, 2008]), the primary endpoint was designed to be evaluated at "Week 27."

The criterion for efficacy in which the lower limit of 95% CI of the hematological response rate at Week 27 should be >15% was established based on the following findings and medical expert's comments: (1) At the time of the study planning, the major drug therapy for patients with AA who did not sufficiently respond to conventional treatments (ATG/CsA combination therapy) was ATG, which meant re-administration; (2) the response rate of ATG in a Japanese clinical study[6)] was 17.9% ("Review Report of Thymoglobulin for Intravenous Infusions 25 mg" [dated May 15, 2008]); and (3) the response rate of re-administered ATG in patients who had not responded to initial ATG was reported to be 17% (2 of 12) of patients (Reference Guideline for Clinical Practice on AA, revised version 2014).

In the concerned global study, the hematological response rate at Week 27 [95% CI], the primary endpoint, was 83.9% (26 of 31) of patients [66.3, 94.5], and the lower limit of the 95% CI exceeded 15%, the pre-determined threshold (Table 12). Based on the above, romiplostim is demonstrated to have the efficacy in the treatment of patients with AA who has not sufficiently responded to conventional treatments.

PMDA considers that there is no particular problem with the primary endpoint in the global phase II/III study, which was established as the hematological response rate at Week 27. The hematological response

6) Percentage of patients showing a response or more remarkable response ("complete response" means a change in symptoms from severe to mild or a change in symptoms from severe to moderate or from moderate to mild and an increase in Hb level by 2 g/dL without blood transfusion; "response" means unchanged symptoms of severe or moderate and an increase in Hb level by 2 g/dL without blood transfusion; "slight response" means a change in symptoms from severe to moderate or from moderate to mild and an increase in Hb level by <2 g/dL without blood transfusion, and "no response" means a condition that is not applicable to that of the complete response, response, or slight response).

rate at Week 27 [95% CI] was 83.9% (26 of 31) of patients [66.3, 94.5] in the concerned global study, and the lower limit of the 95% CI exceeded the pre-determined threshold. Romiplostim is expected to have the efficacy in the treatment of patients with AA who has not sufficiently responded to conventional treatments.

### 7.R.1.3 Major secondary endpoints

The applicant's explanation about results on the major secondary endpoints in the global phase II/III study:

Table 15 shows results on the secondary endpoints in this study, "the platelet response rate, erythrocyte response rate, and neutrophil response rate at Week 27." A certain response was observed in any blood cell lineage. Although the neutrophil response rate was lower in the Japanese population than in the Korean population, a reason for the concerned difference was considered that the percentage of patients who had had the baseline neutrophil count ≥1,000/μL and were thus excluded from the efficacy evaluation (no response) owing to a failure to meet the criteria for a neutrophil response (Table 10) was higher in the Japanese subpopulation (11 of 24 patients [45.8%]) than in the Korean subpopulation (1 of 7 patients [14.3%]).[7)]

**Table 15. Platelet response rate, erythrocyte response rate, and neutrophil response rate at Week 27 (global phase II/III study, FAS)**

| | Japanese subpopulation (n = 24) | Korean subpopulation (n = 7) | Overall populations (n = 31) |
|---|---|---|---|
| Hematological response rate | 79.2 (19) [57.8, 92.9] | 100 (7) [59.0, 100] | 83.9 (26) [66.3, 94.5] |
| Platelet response rate | 66.7 (16) [44.7, 84.4] | 57.1 (4) [18.4, 90.1] | 64.5 (20) [45.4, 80.8] |
| Erythrocyte response rate | 75.0 (18) [53.3, 90.2] | 71.4 (5) [29.0, 96.3] | 74.2 (23) [55.4, 88.1] |
| Neutrophil response rate | 29.2 (7) [12.6, 51.1] | 71.4 (5) [29.0, 96.3] | 38.7 (12) [21.8, 57.8] |

Response rate (%) (number of responders) [95% CI]. Patients who discontinued the study or patients with missing values were handled as non-responders.

Tables 16 and 17 show changes in hematological response and response of each blood cell lineage in the concerned global study. The hematological response rate at Week 53 in overall populations was 80.6% (25 of 31) of patients. The hematological response and response of each blood cell lineage were maintained at a certain level even at Week 27 thereafter.

**Table 16. Changes in hematological response and response of each blood cell lineage (global phase II/III study, all populations, FAS)**

| | Week 13 | Week 27 | Week 40 | Week 53 |
|---|---|---|---|---|
| | Overall populations (n = 31) | | | |
| Hematological response | 77.4 (24) | 83.9 (26) | 80.6 (25) | 80.6 (25) |
| Platelet response | 58.1 (18) | 64.5 (20) | 71.0 (22) | 64.5 (20) |
| Erythrocyte response | 58.1 (18) | 74.2 (23) | 67.7 (21) | 67.7 (21) |
| Neutrophil response | 41.9 (13) | 38.7 (12) | 45.2 (14) | 48.4 (15) |
| Responded in ≥2 lineages | 58.1 (18) | 67.7 (21) | 71.0 (22) | 61.3 (19) |
| Platelet/erythrocyte | 41.9 (13) | 58.1 (18) | 64.5 (20) | 54.8 (17) |
| Platelet/neutrophil | 29.0 (9) | 29.0 (9) | 35.5 (11) | 41.9 (13) |
| Erythrocyte/neutrophil | 32.3 (10) | 32.3 (10) | 35.5 (11) | 41.9 (13) |
| Responded in all 3 lineages | 22.6 (7) | 25.8 (8) | 32.3 (10) | 38.7 (12) |

Responder percentage (%) (number of responders). Patients who discontinued the study or patients with missing values were handled as non-responders.

7) In the patients who had had the baseline neutrophil count <1,000/μL, the "neutrophil response rate at Week 27" was 53.8% (7 of 13) of patients in the Japanese subpopulation and 83.3% (5 of 6) of patients in the Korean subpopulation.

**Table 17. Changes in hematological response and response of each blood cell lineage (global phase II/III study, Japanese and Korean subpopulations, FAS)**

| | Week 13 | | Week 27 | | Week 40 | | Week 53 | |
|---|---|---|---|---|---|---|---|---|
| | Japanese sub-population (n = 24) | Korean sub-population (n = 7) | Japanese sub-population (n = 24) | Korean sub-population (n = 7) | Japanese sub-population (n = 24) | Korean sub-population (n = 7) | Japanese sub-population (n = 24) | Korean sub-population (n = 7) |
| Hematological response | 83.3 (20) | 57.1 (4) | 79.2 (19) | 100 (7) | 79.2 (19) | 85.7 (6) | 83.3 (20) | 71.4 (5) |
| Platelet response | 62.5 (15) | 42.9 (3) | 66.7 (16) | 57.1 (4) | 70.8 (17) | 71.4 (5) | 66.7 (16) | 57.1 (4) |
| Erythrocyte response | 58.3 (14) | 57.1 (4) | 75.0 (18) | 71.4 (5) | 66.7 (16) | 71.4 (5) | 66.7 (16) | 71.4 (5) |
| Neutrophil response | 41.7 (10) | 42.9 (3) | 29.2 (7) | 71.4 (5) | 41.7 (10) | 57.1 (4) | 45.8 (11) | 57.1 (4) |
| Responded in ≥2 lineages | 58.3 (14) | 57.1 (4) | 70.8 (17) | 57.1 (4) | 70.8 (17) | 71.4 (5) | 62.5 (15) | 57.1 (4) |
| Platelet/erythrocyte | 41.7 (10) | 42.9 (3) | 62.5 (15) | 42.9 (3) | 66.7 (16) | 57.1 (4) | 54.2 (13) | 57.1 (4) |
| Platelet/neutrophil | 29.2 (7) | 28.6 (2) | 25.0 (6) | 42.9 (3) | 33.3 (8) | 42.9 (3) | 37.5 (9) | 57.1 (4) |
| Erythrocyte/neutrophil | 29.2 (7) | 42.9 (3) | 25.0 (6) | 57.1 (4) | 29.2 (7) | 57.1 (4) | 37.5 (9) | 57.1 (4) |
| Responded in all 3 lineages | 20.8 (5) | 28.6 (2) | 20.8 (5) | 42.9 (3) | 29.2 (7) | 42.9 (3) | 33.3 (8) | 57.1 (4) |

Responder percentage (%) (number of responders). Patients who discontinued the study or patients with missing values were handled as non-responders.

The time to hematological response (median) [95% CI] determined according to the Kaplan-Meier method was 37.0 days [36.0, 44.0] in all patients, 37.5 days [35.0, 44.0] in the Japanese subpopulation, and 36.0 days [20.0, 53.0] in the Korean subpopulation.

A total of 15 patients (12 Japanese, 3 Koreans) received platelet transfusion within 8 weeks before the first dose of romiplostim. Of these, 80.0% (12 of 15) of all patients, 83.3% (10 of 12) of patients in the Japanese subpopulation, and 66.7% (2 of 3) of patients in the Korean subpopulation achieved weaning from platelet transfusion or reduced volume of platelet transfusion by Week 53.[8)]

A total of 20 patients (14 Japanese, 6 Koreans) received red blood cell transfusion within 8 weeks before the first dose of romiplostim. Of these, 90.0% (18 of 20) of all patients, 92.9% (13 of 14) of patients in the Japanese subpopulation, and 83.3% (5 of 6) of patients in the Korean subpopulation achieved weaning from red blood cell transfusion or reduced volume of red blood cell transfusion by Week 53.[9)]

PMDA has confirmed that results on the major secondary endpoints in the global phase II/III study are not inconsistent with those on the primary endpoint. In addition, PMDA has confirmed that the hematological response and response of each blood cell lineage tend to be maintained at a certain level even at Week 27 thereafter.

### 7.R.1.4 Efficacy by patient characteristic

The applicant's explanation about the efficacy by patient characteristic in the global phase II/III study:
Table 18 shows results on the "hematological response rate at Week 27" by patient characteristic in the global phase II/III study. Although the number of patients in each subgroup is limited, making adequate investigation difficult, a certain response was observed in any subgroup.

8) During a period of 8 consecutive weeks, no platelet transfusion was performed, or the volume of platelet transfusion was reduced from that within 8 weeks before start of the treatment.
9) During a period of 8 consecutive weeks, no red blood cell transfusion was performed, or the volume of red blood cell transfusion was reduced from that within 8 weeks before start of the treatment.

**Table 18. Hematological response rate at Week 27 by patient characteristics (global phase II/III study, FAS)**

| Stratification item | Category | Hematological response rate at Week 27 | Stratification item | Category | Hematological response rate at Week 27 |
|---|---|---|---|---|---|
| Age | <65 years | 82.1 (23/28) | Severity of AA | Stage ≤2 | 87.5 (7/8) |
| | ≥65 years | 100 (3/3) | | Stage ≥3 | 82.6 (19/23) |
| Sex | Male | 88.9 (8/9) | Prior treatment with ATG | Yes | 77.3 (17/22) |
| | Female | 81.8 (18/22) | | No | 100 (9/9) |
| Baseline platelet count | <15,000/μL | 88.2 (15/17) | Concomitant use of CsA and anabolic steroid | Yes | 80.0 (16/20) |
| | ≥15,000/μL | 78.6 (11/14) | | No | 90.9 (10/11) |

Response rate (%) (number of responders/number of patients evaluated). Patients who discontinued the study or patients with missing values were handled as non-responders.

Concerning the efficacy by patient characteristics, PMDA has confirmed that any specific subgroup does not present any trend that would raise a clinically relevant problem.

### 7.R.2 Safety

Based on the review in Sections 7.R.2.1 to 7.R.2.5 below, PMDA considers that romiplostim has the acceptable safety in the treatment of AA that has not sufficiently responded to conventional treatments. The number of patients enrolled in the clinical studies in patients with AA is extremely limited, therefore, post-marketing surveillance, etc. should be conducted to collect information about events related to platelet increased and thromboembolism, platelet decreased and haemorrhage after discontinuation or end of the treatment, events related to hematologic malignancy as well as events related to bone marrow fibrogenesis.

#### 7.R.2.1 Adverse events in the global phase II/III study

Table 19 shows incidences of adverse events in the global phase II/III study. Nasopharyngitis, upper respiratory tract infection, pyrexia, headache, muscle spasms, and diarrhoea occurred in ≥10% of all patients, but all of these events were mild or moderate in severity, except for upper respiratory tract infection in 1 patient. Although upper respiratory tract infection in 1 patient was severe, a causal relationship to romiplostim was denied, and it resolved.

Serious adverse events occurred in 2 patients in the Japanese subpopulation (sepsis and spondylitis in 1 patient each), but a causal relationship to romiplostim was denied for either event. No serious adverse events occurred in the Korean subpopulation.

Adverse drug reactions occurred in 66.7% (16 of 24) of patients in the Japanese subpopulation and 14.3% (1 of 7) of patients in the Korean subpopulation. Although the incidence of adverse drug reactions was higher in the Japanese subpopulation than in the Korean subpopulation, all of the reactions were mild or moderate in severity except for alanine aminotransferase (ALT) increased in 1 patient. ALT increased in 1 patient was severe but was not a serious event that is potentially life-threatening or requires inpatient hospitalization, and it resolved.

Based on the above, no clinically relevant problems were observed in either the Japanese or Korean subpopulation.

**Table 19. Incidences of adverse events reported by ≥10% of all patients (global phase II/III study)**

| | Japanese subpopulation (n = 24) | Korean subpopulation (n = 7) | Overall patients (n = 31) |
|---|---|---|---|
| Adverse events | 95.8 (23) | 85.7 (6) | 93.5 (29) |
| Adverse drug reactions | 66.7 (16) | 14.3 (1) | 54.8 (17) |
| Death | 0 (0) | 0 (0) | 0 (0) |
| Serious adverse events | 8.3 (2) | 0 (0) | 6.5 (2) |
| Adverse events leading to discontinuation | 0 (0) | 0 (0) | 0 (0) |
| Nasopharyngitis | 37.5 (9) | 57.1 (4) | 41.9 (13) |
| Upper respiratory tract infection | 29.2 (7) | 14.3 (1) | 25.8 (8) |
| Pyrexia | 20.8 (5) | 14.3 (1) | 19.4 (6) |
| Headache | 20.8 (5) | 0 (0) | 16.1 (5) |
| Muscle spasms | 16.7 (4) | 0 (0) | 12.9 (4) |
| Diarrhoea | 12.5 (3) | 14.3 (1) | 12.9 (4) |

MedDRA ver. 20.1. Incidence (%) (number of patients with the event).

Table 20 shows incidence of adverse events by the treatment period in the global phase II/III study. There was no trend of events in any period that would raise a particular problem.

**Table 20. Incidence of adverse events by period (global phase II/III study)**

| | Days 1-85 (n = 31) | Days 86-183 (n = 31) | Days 184-274 (n = 28) | Days 275-365 (n = 27) | Day 365 thereafter (n = 27) | Total (n = 31) |
|---|---|---|---|---|---|---|
| Adverse events | 83.9 (26) | 64.5 (20) | 46.4 (13) | 81.5 (22) | 14.8 (4) | 93.5 (29) |
| Adverse drug reactions | 38.7 (12) | 25.8 (8) | 10.7 (3) | 11.1 (3) | 0 (0) | 54.8 (17) |
| Death | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Serious adverse events | 0 (0) | 0 (0) | 7.1 (2) | 0 (0) | 0 (0) | 6.9 (2) |
| Adverse events leading to treatment discontinuation | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Nasopharyngitis | 19.4 (6) | 19.4 (6) | 14.3 (4) | 11.1 (3) | 0 (0) | 41.9 (13) |
| Upper respiratory tract infection | 9.7 (3) | 9.7 (3) | 10.7 (3) | 14.8 (4) | 0 (0) | 25.8 (8) |
| Pyrexia | 3.2 (1) | 9.7 (3) | 3.6 (1) | 7.4 (2) | 3.7 (1) | 19.4 (6) |
| Headache | 9.7 (3) | 0 (0) | 3.6 (1) | 3.7 (1) | 3.7 (1) | 16.1 (5) |
| Diarrhoea | 3.2 (1) | 3.2 (1) | 3.6 (1) | 3.7 (1) | 0 (0) | 12.9 (4) |
| Muscle spasms | 3.2 (1) | 6.5 (2) | 0 (0) | 3.7 (1) | 0 (0) | 12.9 (4) |

MedDRA ver. 20.1. Incidence (%) (number of patients with the event). Events of which the total incidence was ≥10% are individually tabulated. If the same event occurred in different periods, 1 patient was counted for each of these periods.

PMDA has confirmed that the incidences of adverse events in the global phase II/III study do not present any trend that would raise a clinically relevant problem.

### 7.R.2.2 Comparison with results from clinical studies in patients with chronic idiopathic thrombocytopenic purpura

The applicant's explanation about the safety of romiplostim in patients with AA in comparison with results from clinical studies in patients with chronic idiopathic thrombocytopenic purpura (ITP), for which an indication has been already approved:

Table 21 shows incidences of adverse events in the global phase II/III study in patients with AA and those in the pooled data from clinical studies[10)] in patients with chronic ITP. There was no increasing trend of adverse events in the study in patients with AA that would raise a clinically relevant problem, when compared with those in studies in patients with chronic ITP.

10) Japanese phase II study (20050162), Japanese phase III study (20060216), Japanese long-term treatment study (20060113), foreign phase I/II study (20000137A), foreign phase I/II study (20010218), foreign phase I/II study (20060195), foreign phase II study (20000137B), foreign phase III study (20030105), foreign phase III study (20030212), foreign phase IIIb study (20040209), foreign phase IIIb study (20060131), foreign phase III study (20050123), and foreign long-term treatment study (20030213)

Based on the above, the safety profile is considered to have no large differences between patients with AA who have not sufficiently responded to conventional treatments and patients with chronic ITP.

**Table 21. Incidences of adverse events in the study in patients with AA and in studies in patients with chronic ITP[a)]**

| | Patients with AA (n = 31) | Patients with ITP (n = 653) | | Patients with AA (n = 31) | Patients with ITP (n = 653) |
|---|---|---|---|---|---|
| All adverse events | 678.0 (205) | 1341.4 (12,361) | Abdominal pain upper | 19.8 (6) | 6.8 (63) |
| Nasopharyngitis | 76.1 (23) | 35.9 (331) | Gingival bleeding | 19.8 (6) | 13.3 (123) |
| Upper respiratory tract infection | 52.9 (16) | 23.1 (213) | Diarrhoea | 13.2 (4) | 26.0 (240) |
| Headache | 36.4 (11) | 79.2 (730) | Malaise | 13.2 (4) | 2.9 (27) |
| Pyrexia | 26.5 (8) | 13.0 (120) | Muscle spasms | 13.2 (4) | 11.3 (104) |
| Chills | 23.2 (7) | 4.9 (45) | Pain in extremity | 13.2 (4) | 19.3 (178) |
| Rash | 23.2 (7) | 13.0 (120) | Oropharyngeal pain | 13.2 (4) | 15.2 (140) |

MedDRA ver. 20.1 (global phase II/III study in patients with AA), ver. 12.0 (clinical studies in patients with chronic ITP)
Incidence rate per 100 patient-years (number of events)
a) Incidence rate per 100 patient-years of adverse events reported by ≥10% of patients in the study in patients with AA

PMDA has confirmed that when compared with the safety profile in patients with chronic ITP, for which an indication has been already approved, no clinically relevant differences are observed in the global phase II/III study in patients with AA. In addition, no events that would raise a particular problem were observed in the foreign phase II study [see Section 7.1]. Accordingly, PMDA considers that the safety of romiplostim in patients with AA who have not sufficiently responded to conventional treatments is acceptable when it is used under the same safety measures as those taken in patients with chronic ITP.

### 7.R.2.3 Noteworthy adverse events

PMDA reviewed the following noteworthy adverse events based on the mechanism of action and results from non-clinical and clinical studies of romiplostim as described in Sections 7.R.2.3.1 to 7.R.2.3.5: Events related to platelet count increased and thromboembolism, platelet decreased and haemorrhage after discontinuation or end of the treatment, events related to hematologic malignancy and chromosome abnormality, events related to bone marrow fibrogenesis as well as events related to hypersensitivity.

#### 7.R.2.3.1 Events related to platelet count increased and thromboembolism

An excessively increased platelet count in a patient receiving romiplostim may lead to an increased risk of thrombosis or thromboembolism, and the current package insert of romiplostim has cautioned about thromboembolism. In addition, an event related to thromboembolism for which a causal relationship to romiplostim could not be ruled out was reported by 1 patient with chronic ITP after the market launch. Concerning the above, PMDA asked the applicant to explain incidence of events related to platelet count increased and thromboembolism in clinical studies in patients with AA.

The applicant's explanation:

Events related to platelet count increased were extracted from data in clinical studies in patients with AA by preferred term (PT) in MedDRA (platelet count increased and thrombocytosis). In addition, as events related to thromboembolism, the following events classified under Standardized MedDRA Query (SMQ) in MedDRA were evaluated: "Embolic and thrombotic events, arterial (narrow)," "embolic and

thrombotic events, venous (narrow),” and “embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (narrow).”

In the global phase II/III study, an event related to platelet count increased occurred in 3.2% (1 of 31) of patients (platelet count increased). Although the concerned event was classified as an adverse drug reaction, it resolved following dose reduction of romiplostim. In the global study, no events related to thromboembolism occurred. Furthermore, in the foreign phase II study, neither events related to platelet count increased nor thromboembolism occurred.

PMDA has confirmed that events related to platelet count increased and thromboembolism in the global phase II/III study, etc. do not present any trend that would raise a particular problem. However, a caution about a risk of thromboembolism should be exercised, as noted in the current package insert, for the following reasons: The number of patients enrolled in the clinical studies in patients with AA is extremely limited; romiplostim has a platelet-increasing effect; and an event related to thromboembolism for which a causal relationship to romiplostim could not be ruled out was reported by a patient with chronic ITP after the market launch. In addition, information about incidences of events related to platelet count increased and thromboembolism should be continuously collected through a post-marketing surveillance, etc.

**7.R.2.3.2 Platelet decreased and haemorrhage after discontinuation or end of the treatment**

The platelet count after discontinuation of the romiplostim treatment was found to be lower than the baseline count in some patients in clinical studies in patients with chronic ITP. In addition, a risk of haemorrhage may be increased in association with platelet decreased, and the current package insert of romiplostim has cautioned about platelet decreased and haemorrhage after discontinuation of the treatment. Concerning the above, PMDA asked the applicant to explain events related to platelet decreased and haemorrhage after discontinuation or end of the romiplostim treatment in clinical studies in patients with AA.

The applicant’s explanation:
As events related to platelet decreased, events classified under MedDRA SMQ “haematopoietic thrombocytopenia (broad)” were evaluated in clinical studies in patients with AA. In addition, as events related to haemorrhage, events classified under MedDRA SMQ “haemorrhage laboratory terms (broad)” and “haemorrhage terms (excluding laboratory terms) (broad)” were evaluated.

In the global phase II/III study, no events related to platelet decreased occurred after discontinuation or end of the treatment. In the foreign phase II study, an event related to haemorrhage after discontinuation or end of the treatment occurred in 1 patient (purpura), but it was mild, and a causal relationship to romiplostim was denied.

PMDA has confirmed that events related to thrombocytopenia and haemorrhage after end of the treatment in the global phase II/III study, etc. do not present any trend that would raise a particular problem. As noted in the current package insert, however, a caution about an increased risk of haemorrhage after discontinuation or end of the romiplostim treatment should be exercised because the

number of patients enrolled in the clinical studies in patients with AA is extremely limited; and the platelet count after discontinuation of the romiplostim treatment was found to be lower than the baseline count in some patients in clinical studies in patients with chronic ITP. In addition, information about incidences of events related to platelet decreased and haemorrhage after discontinuation or end of the romiplostim treatment should be continuously collected through a post-marketing surveillance, etc.

#### 7.R.2.3.3 Events related to hematologic malignancy and chromosome abnormality

A caution about events related to hematologic malignancy has been provided in the current package insert of romiplostim for the following reasons: TPO stimulates growth of TPO-receptor positive acute myeloid leukemia cells (*Blood.* 2006;107:2525-30, *Leuk Res.* 1998;22:527-35); and hematologic malignancy was reported in a foreign clinical study of romiplostim in patients with chronic ITP. In addition, AA is known to progress to myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) in some patients (Reference Guideline for Clinical Practice on AA 2018), and PMDA asked the applicant to explain incidences of events related to hematologic malignancy and chromosome abnormalities in bone marrow examinations in clinical studies in patients with AA.

The applicant's explanation:
As events related to hematologic malignancy, events classified under MedDRA SMQ "haematological malignant tumours (broad)" were evaluated in clinical studies in patients with AA.

In the global phase II/III study, no events related to hematologic malignancy occurred. In the concerned study, chromosome abnormalities were found in 2 patients[11)] by bone marrow examinations, but no progression to MDS or AML was observed in either patient. In addition, in the foreign phase II study, no events related to hematologic malignancy occurred, and chromosome abnormality was found in 1 patient[12)] by bone marrow examinations, but no progression to MDS or AML was observed.

PMDA has confirmed that events related to hematologic malignancy and chromosome abnormalities in bone marrow examinations in the global phase II/III study, etc. do not present any trend that would raise a particular problem. Information about incidences of events related to hematologic malignancy, however, should be continuously collected through a post-marketing surveillance, etc. for the following reasons: The number of patients included in the clinical studies in patients with AA is extremely limited; hematologic malignancy was reported in foreign studies in patients with chronic ITP; AA may progress to MDS or AML in some patients while being followed up (Reference Guideline for Clinical Practice on AA 2018).

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11) In either of 2 patients, no abnormalities were found in chromosome banding at the screening. In 1 patient, 7 chromosomes (chromosomes 3, 4, 14, 16, 17, 19, and 21) were found increased in 1 of 9 dividing cells at Week 27. In the concerned patient, a neutrophil response was observed and chromosome 7 of which abnormality would lead to poor outcome was normal, thus, the trial was continued, and at Week 53, no chromosome abnormalities were found. In the other 1 patient, no platelet response was observed and the trial was discontinued at Week 16. Chromosome abnormality was found in an examination at the discontinuation. When 20 dividing cells were examined, deletion in chromosome 7 was found in 4 cells, and deletion in chromosome 7 and long arm (position unknown) in chromosome 5 were found in 1 cell. In addition, monosomy 7 was found in 50% of the cells. In the concerned patient, no progression to MDS or AML occurred, and thus deletion in chromosome 7 was considered as an event occurring in the course of the primary disease.

12) When 20 dividing cells were examined at the screening, trisomy 8 was found in 5 cells. In the examinations after administration of romiplostim (Weeks 25, 53, 77, and 129), trisomy 8 was found in 2 to 6 cells as found at the screening. When 20 dividing cells were examined at the last examination (Week 156), trisomy 8 was found in 6 cells, and trisomy 8 and duplication of long arm q12-q44 in chromosome 1 were found in 2 cells.

#### 7.R.2.3.4 Events related to bone marrow fibrogenesis

Concerning events related to bone marrow fibrogenesis, the current package insert of romiplostim has a caution statement that increased bone marrow reticulin associated with romiplostim may occur, resulting in bone marrow fibrogenesis.[3)] In addition, increased bone marrow reticulin leading to the treatment discontinuation occurred in 1 patient in a clinical study in patients with chronic ITP. Concerning the above, PMDA asked the applicant to explain incidences of events related to bone marrow fibrogenesis in clinical studies in patients with AA and grading results for reticulin by bone marrow examinations.

The applicant's explanation:
Events related to bone marrow fibrogenesis were extracted from data in clinical studies in patients with AA by MedDRA PTs (reticulin increased, bone marrow reticulin fibrosis, and myelofibrosis).

In the global phase II/III study, Grade for reticulin worsened in 2 patients after administration of romiplostim.[13)] In the foreign phase II study, Grade for reticulin worsened in 2 patients after administration of romiplostim as well.[14)] No events related to bone marrow fibrogenesis, however, occurred in either study.

PMDA has confirmed that events related to bone marrow fibrogenesis in the global phase II/III study do not present any trend that would raise a particular problem. As noted in the current package insert, however, a caution about potential onset of bone marrow fibrogenesis should be exercised because the number of patients enrolled in the clinical studies in patients with AA is extremely limited; increased bone marrow reticulin associated with romiplostim may occur, and bone marrow fibrogenesis may further occur; and Grade for reticulin worsened in some patients in clinical studies in patients with AA. In addition, information about incidences of events related to bone marrow fibrogenesis should be continuously collected through a post-marketing surveillance, etc.

#### 7.R.2.3.5 Events related to hypersensitivity

Romiplostim is formulated as a peptide drug product for subcutaneous injection and hypersensitivity may occur. PMDA asked the applicant to explain incidences of events related to hypersensitivity in clinical studies in patients with AA.

The applicant's explanation:
Events related to hypersensitivity classified under MedDRA SMQ "hypersensitivity (narrow)" were evaluated in clinical studies in patients with AA.

In the global phase II/III study, events related to hypersensitivity occurred in 22.6% (7 of 31) of patients, and events related to hypersensitivity reported by ≥2 patients were allergic transfusion reaction, rash, and urticaria in 6.5% each (2 of 31) of patients. A causal relationship to romiplostim was denied for any of the events related to hypersensitivity, and all of these were mild or moderate in severity. In the foreign phase II study, events related to hypersensitivity occurred in 25.9% (9 of 35) of patients overall (urticaria

13) In the global phase II/III study, a worsening change for reticulin from Grade 0 to 1 (Week 53) occurred in 2 patients. Either change was assessed to have no clinical significance by the investigator.
14) In the foreign phase II study, worsening changes for reticulin from Grade 0 to 2 (Week 53) and from Grade 1 to 3 (Week 53) occurred in 1 patient each. Either change was assessed to have no clinical significance by the investigator.

in 4 patients, rash in 2 patients, and dermatitis, eczema, face oedema, and rash pustular in 1 patient each [some patients experienced multiple events]). Events related to hypersensitivity reported by ≥2 patients in the concerned foreign study were urticaria in 11.4% (4 of 35) of patients (2 each in the romiplostim 3 μg/kg group and 6 μg/kg group) and rash in 5.7% (2 of 35) of patients (2 in the 6 μg/kg group). A causal relationship to romiplostim was denied for any of the events related to hypersensitivity, and all of these were mild or moderate in severity, except for urticaria in 1 patient in the 3 μg/kg group and rash in 1 patient in the 6 μg/kg group.

PMDA considers that there are no clinically relevant problems with events related to hypersensitivity at present because a causal relationship to romiplostim was denied for any of these events, and most of these were mild or moderate in severity.

#### 7.R.2.4 Neutralizing antibodies against romiplostim or TPO

The applicant's explanation about development of neutralizing antibody against romiplostim or TPO in clinical studies in patients with AA:
In the global phase II/III study, 3.2% (1 of 31) of patients were positive for anti-romiplostim antibody, and 3.2% (1 of 31) of patients were positive for anti-TPO antibody. Either of the patients, however, was negative for neutralizing antibody against romiplostim or TPO. The efficacy and safety were not affected [see Section 6.2.1].

PMDA has confirmed that there are no trends for development of neutralizing antibodies against romiplostim and TPO in patients with AA to affect the efficacy and safety of romiplostim at present.

#### 7.R.2.5 Post-marketing safety information

The applicant's explanation about post-marketing safety information about romiplostim:
As of March 2019, romiplostim has been approved in ≥60 countries including Japan, the US, and EU countries since it was first approved for the indication of chronic ITP in Australia in July 2008. Based on the latest periodic benefit risk evaluation report (PBRER) and periodic safety update report (PSUR) (PBRER/PSUR, covering from August 1, 2017 to July 31, 2018), cumulative post-marketing use experience was estimated to be approximately [redacted] patient-years worldwide. Of 20,296 post-marketing adverse events listed in the latest PBRER/PSUR, 13,116 were serious adverse drug reactions, mainly including 665 events of platelet count decreased and 463 events of thrombocytopenia, but both were known adverse drug reactions.

According to the latest periodic safety reports (covering from July 31, 2017-July 30, 2018), the specified drug use-results survey in patients with chronic ITP, currently ongoing in Japan, collected information from 1,695 patients between the launch in Japan (April 13, 2011) and the end of a period covered by the latest periodic safety reports (July 30, 2018), and of the above-mentioned 1,695 patients, who were included in the safety analysis set, 436 patients (25.7%) experienced adverse drug reactions. The major adverse drug reactions were white blood cell count increased (3.1%, 52 patients), headache (1.7%, 29 patients), anaemia (1.6%, 27 patients), platelet count decreased (1.4%, 23 patients), malaise (1.2%, 21 patients), and neutrophil count increased (1.1%, 18 patients). All of these were known.

Based on the above, the currently available post-marketing safety information about romiplostim do not present any additional event that may affect the safety profile of romiplostim.

PMDA has confirmed that the currently available post-marketing safety information about romiplostim used for the approved indication in and outside Japan do not present any event that may raise a particular problem.

### 7.R.3 Clinical positioning

The applicant's explanation about clinical positioning of romiplostim:
Treatment strategy of AA is determined by age, severity, availability of a donor, responsiveness to immunosuppressive therapy, etc. (Reference Guideline for Clinical Practice on AA 2018). For patients aged ≥40 years and patients without any HLA-matched sibling donor, immunosuppressive therapy including ATG/CsA is indicated. If a response to the initial immunosuppressive therapy is not sufficient, re-administration of ATG/CsA or addition of EPAG (if not used in the initial therapy) may be considered. Because romiplostim is a TPO receptor agonist as with EPAG, romiplostim is considered to be positioned in the same category of the treatment algorithm for AA patients who have not sufficiently responded to conventional treatments.

Romiplostim has a TPO receptor agonistic action as EPAG does, and the global study in patients with AA who did not sufficiently respond to conventional treatments showed positive results. PMDA, therefore, considers that romiplostim is positioned as a drug inferred to be used in patients with AA who have not sufficiently responded to conventional treatments as with EPAG. In addition, romiplostim can be offered as one treatment option to patients with AA who have not sufficiently responded to conventional treatments.

### 7.R.4 Indication

PMDA considers that romiplostim is expected to have the efficacy based on results from the global phase II/III study in patients with AA who did not sufficiently respond to conventional treatments [see Section 7.R.1], and the safety is acceptable [see Section 7.R.2]. In consideration that the conducted clinical study enrolled patients with AA who did not sufficiently respond to conventional treatments, the indication of romiplostim should be changed from the proposed "aplastic anemia" to "aplastic anemia that has not responded sufficiently to conventional treatments." The use of romiplostim should be decided in accordance with the Reference Guideline for Clinical Practice on AA.

### 7.R.5 Dosage and administration

The applicant's explanation about the dosage and administration of romiplostim:
In the foreign phase II study, romiplostim was administered subcutaneously once weekly at 1, 3, 6 or 10 μg/kg for 8 weeks from Weeks 1 to 8, and the platelet response rate at Week 9 in the 10 μg/kg group was the highest at 70.0% (7 of 10 patients) among the treatment groups. At a dose <10 μg/kg, on the other hand, romiplostim did not have the expected efficacy in patients with AA [see Section 7.1]. In the global phase II/III study, therefore, the starting dose of romiplostim was selected at 10 μg/kg. In the foreign phase II study, the dose of romiplostim at Week 9 thereafter was titrated within a range from 1 to 20 μg/kg according to the platelet count and adverse events as appropriate. In the foreign phase II

study, the dose of romiplostim was increased to 20 μg/kg in 88.6% (31 of 35) of patients, but there were no safety problems. In the global phase II/III study, the highest dose was selected at 20 μg/kg, and the dose of romiplostim was titrated according to the blood count and adverse events as appropriate (Table 11).

Table 22 shows distribution of the dose (percentage of patients) at each timepoint in the global phase II/III study.

For the efficacy, the hematological response rate at Week 53 by dose of romiplostim was 100% (4 of 4) of patients at 5 μg/kg, 100% (2 of 2) of patients at 10 μg/kg, 100% (3 of 3) of patients at 15 μg/kg, and 92.9% (13 of 14 patients) at 20 μg/kg, showing no large differences in the hematological response rate among doses.

For the safety, the incidence of adverse events until Week 53 by dose at the time of onset was 33.3% (2 of 6) of patients at the time of suspension, 62.5% (5 of 8) of patients at 5 μg/kg, 58.1% (18 of 31) of patients at 10 μg/kg, 59.3% (16 of 27) of patients at 15 μg/kg, and 90.5% (19 of 21) of patients at 20 μg/kg. The incidence of adverse drug reactions by dose at the time of onset was 0% (0 of 6) of patients at the time of suspension, 12.5% (1 of 8) of patients at 5 μg/kg, 29.0% (9 of 31) of patients at 10 μg/kg, 22.2% (6 of 27) of patients at 15 μg/kg, and 28.6% (6 of 21) of patients at 20 μg/kg. There were no large differences in incidence of adverse drug reactions among doses at the time of onset.

Based on the above, it was considered appropriate to establish the dosage and administration of romiplostim as done in the global phase II/III study, in which romiplostim was started at 10 μg/kg, and the once-weekly subcutaneous dose was then titrated up to 20 μg/kg according to the patient's condition (blood count, etc.) as appropriate. In addition, it was considered acceptable to establish the dose titration method of romiplostim as done in the global phase II/III study.

**Table 22. Distribution of dose of romiplostim (global phase II/III study)**

| Treatment period | Dose of romiplostim (μg/kg) | | | | |
|---|---|---|---|---|---|
| | 0 | 5 | 10 | 15 | 20 |
| Week 13 (n = 31) | 3.2 (1) | 0 (0) | 9.7 (3) | 32.3 (10) | 54.8 (17) |
| Week 27 (n = 28) | 7.1 (2) | 3.6 (1) | 10.7 (3) | 21.4 (6) | 57.1 (16) |
| Week 40 (n = 27) | 3.7 (1) | 11.1 (3) | 11.1 (3) | 25.9 (7) | 48.1 (13) |
| Week 53 (n = 27) | 14.8 (4) | 14.8 (4) | 7.4 (2) | 11.1 (3) | 51.9 (14) |

Percentage of patients (%) (number of patients)

PMDA has accepted the following dosage and administration of romiplostim: It is started at 10 μg/kg, and the once-weekly subcutaneous dose is then titrated up to 20 μg/kg according to the patient's condition as appropriate. In addition, PMDA has considered that it has no particular problem to establish the dose titration method of romiplostim as done in the global phase II/III study.

### 7.R.6 Post-marketing investigations

The applicant plans a post-marketing specified use-results survey as shown in Table 23.

**Table 23. Outline of specified use-results survey (draft)**

| | |
|---|---|
| Objective | To investigate the long-term safety of romiplostim in clinical use in patients with AA who have not sufficiently responded to conventional treatments |
| Survey method | Central registry system |
| Population | Patients with AA who have not sufficiently responded to conventional treatments |
| Planned sample size | 60 patients (included in the analysis) |
| Survey period | 4 years (registration period, 2 years) |
| Observation period | 1 year |
| Main survey items | • Patient characteristics (age, severity of AA and prior treatment, medical history, comorbidities, etc.)<br>• Details of treatment with romiplostim (dose, date of initial administration and date of discontinuation, reason for discontinuation, etc.)<br>• Details of platelet transfusion and red blood cell transfusion (dose volume, date of transfusion)<br>• Use of concomitant drugs (name of drugs, reason for use, etc.)<br>• Laboratory values (red blood cell count, Hb level, white blood cell count, platelet count, etc.)<br>• Adverse events (date of onset, seriousness, outcome, causal relationship to romiplostim, treatments, etc.) |

The number of patients enrolled in the global phase II/III study is extremely limited, and PMDA considers that post-marketing information about the following points should be collected:

- Events related to platelet increased and thromboembolism
- Platelet decreased and haemorrhage after discontinuation or end of the treatment
- Events related to hematologic malignancy
- Events related to bone marrow fibrogenesis

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that romiplate is expected to have efficacy in the treatment of aplastic anemia in patients who have not responded sufficiently to conventional treatments, and that romiplate has acceptable safety in view of its benefits. PMDA has concluded that this application may be approved if efficacy, safety, indication, dosage and administration, and post-

marketing investigations are not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

May 15, 2019

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Romiplate for S.C. Injection 250 μg |
| **Non-proprietary Name** | Romiplostim (Genetical Recombination) |
| **Applicant** | Kyowa Hakko Kirin Co., Ltd. |
| **Date of Application** | July 31, 2018 |

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, 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).

### 1.1 Efficacy, safety, indication, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions in Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.4 Indication," and "7.R.5 Dosage and administration" of the Review Report (1).

Based on the above, PMDA instructed the applicant to modify [Indication] and [Dosage and administration] of romiplostim for AA as well as Precautions Concerning Indication and Precautions Concerning Dosage and Administration for AA in the package insert as shown below. The applicant responded appropriately, and PMDA accepted the response.

**Indication**

Aplastic anemia that has not responded sufficiently to conventional treatments

**Precautions Concerning Indication**

Aplastic anemia that has not responded sufficiently to conventional treatments

Romiplostim should be administered to patients considered to be eligible for the treatment with romiplostim in accordance with Reference Guideline for Clinical Practice on Aplastic Anemia, revised version 2018, by a physician who is familiar with the content in the "Clinical Studies" section and adequately understood the efficacy and safety of romiplostim.

**Dosage and Administration**

Aplastic anemia that has not responded sufficiently to conventional treatments

The usual initial adult dosage is 10 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 condition. The maximum dose is 20 μg/kg once weekly.

**Precautions Concerning Dosage and Administration**

Aplastic anemia that has not responded sufficiently to conventional treatments

1. The blood count should be determined basically once weekly when treatment with romiplostim is started and when the dose is titrated. Even when the dose is being maintained, the blood count should be determined basically every 4 weeks.
2. When the dose is titrated, it should be increased or decreased in 5 μg/kg increments usually.
3. A dose increase should be considered, if an increase in platelet count (as a guide, platelet count is increased by ≥20,000/μL from the baseline or is ≥10,000/μL and increased by ≥100% from the baseline, in a patient independent of blood transfusion) is not observed after the same dose has been administered for 4 consecutive weeks.
4. Romiplostim should be used at the minimum dose required for treatment according to the table below.

| Platelet count | Titration method |
|---|---|
| 200,000/μL-400,000/μL | Decrease the dose of romiplostim. |
| >400,000/μL | Suspend the administration. If the platelet count is decreased to 200,000/μL after suspension, resume the administration at the dose lower than that before suspension, in principle.<br>If the dose before suspension is ≤5 μg/kg, and the platelet count is decreased to 50,000/μL, the treatment may be resumed at the same dose as that before suspension. |

5. The dose should be decreased when improvements in 3 blood cell lineages (as a guide, the platelet count is increased to >50,000/μL, the hemoglobin level exceeds 10 g/dL, and the neutrophil count exceeds 1,000/μL, in a patient independent of blood transfusion) continue for ≥8 weeks. If improvements in 3 blood cell lineages are maintained at the decreased dose for 4 weeks, the dose should be decreased further, and then a dose decrease should be considered every 4 weeks (consider suspension, if the dose is ≤5 μg/kg). If any of the 3 blood cell lineages worsen at the decreased dose, a dose increase should be considered (if the treatment has been suspended, it may be resumed at the same dose as that before the suspension).
6. If no improvement is observed in any of 3 blood cell lineages after the once-weekly treatment at a dose up to 20 μg/kg for 8 consecutive weeks, appropriate measures such as discontinuation of the treatment with romiplostim should be taken.

## 1.2 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusions in Section "7.R.6 Post-marketing investigations" of the Review Report (1). The following comments were made by the expert advisors:

- Results from clinical studies in patients with AA are extremely limited, and a post-marketing surveillance should cover all the patients. As romiplostim is likely to promote hematologic malignancy or bone marrow fibrogenesis through activation of TPO receptor, patients with AA

enrolled in the specified use-results survey should be followed up for at least 1 year to collect information about development of hematologic malignancy and bone marrow fibrogenesis in patients receiving romiplostim for an extended period.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for romiplostim should include the safety and efficacy specifications presented in Table 24, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 25 as well as the specified use-results survey presented in Table 26.

**Table 24. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Haemorrhage<br>• Thromboembolism | • Hematologic malignancy<br>• Bone marrow fibrogenesis | • None |
| Efficacy specification | | |
| •None | | |

**Table 25. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Specified use-results survey (chronic ITP)<br>• Early post-marketing phase vigilance (AA)<br>• Specified use-results survey (AA) | • Provision of information obtained through the early post-marketing phase vigilance (AA) |

**Table 26. Outline of specified use-results survey (draft)**

| | |
|---|---|
| Objective | To investigate the long-term safety of romiplostim in clinical use in patients with AA who have not sufficiently responded to conventional treatments |
| Survey method | All-case surveillance |
| Population | Patients with AA who have not sufficiently responded to conventional treatments |
| Planned sample size | All patients |
| Observation period | 1 year (up to 2 years in patients who have continuously received romiplostim for >1 year) |
| Main survey items | • Patient characteristics (age, severity of AA and prior treatment, medical history, comorbidities, etc.)<br>• Details of treatment with romiplostim (dose, date of initial administration and date of discontinuation, reason for discontinuation, etc.)<br>• Details of platelet transfusion and red blood cell transfusion (dose volume, date of transfusion)<br>• Use of concomitant drugs (name of drugs, reason for use, etc.)<br>• Laboratory values (red blood cell count, Hb level, white blood cell count, platelet count, etc.)<br>• Adverse events (date of onset, seriousness, outcome, causal relationship to romiplostim, treatments, etc.) |

## 2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. Since this application is related to the drug with a new active ingredient approved as an orphan drug and intended to add the disease not designated for orphan drugs to the indication of such approved drug, the appropriate re-examination period for the proposed indication as well as corresponding dosage and administration should be 5 years and 10 months.

**Indication**

Chronic idiopathic thrombocytopenic purpura

Aplastic anemia that has not responded sufficiently to conventional treatments

(Underline denotes additions.)

**Dosage and Administration**

Chronic idiopathic thrombocytopenic purpura

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.

Aplastic anemia that has not responded sufficiently to conventional treatments

The usual initial adult dosage is 10 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 condition. The maximum dose is 20 μg/kg once weekly.

(Underline denotes additions.)

**Conditions of Approval**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. 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 characteristics of patients treated with the product. At the same time, the applicant required to collect safety and efficacy data on the product without delay and to take necessary measures to facilitate the proper use of the product.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| AA | Aplastic anemia |
| Adverse drug reaction | Adverse event for which a causal relationship to romiplostim cannot be ruled out |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukemia |
| AST | Aspartate aminotransferase |
| ATG | Anti-human thymocyte globulin |
| ATG/CsA | Anti-human thymocyte globulin/ciclosporin A |
| $AUC_{0\text{-}inf}$ | Area under concentration-time curve up to infinity |
| $AUC_{0\text{-}\tau}$ | Area under concentration-time curve during dose interval |
| $C_{max}$ | Maximum concentration |
| CsA | Ciclosporin A |
| CTD | Common technical document |
| ELISA | Enzyme linked immuno sorbent assay |
| EPAG | Eltrombopag olamine |
| FAS | Full analysis set |
| Fc | Fragment crystallizable |
| Foreign phase II study | Foreign phase II study (CTD 5.3.5.2-1, Study 531-KR001) |
| GCP | Good Clinical Practice |
| G-CSF | Granulocyte-colony stimulating factor |
| Global phase II/III study | Global phase II/III study (CTD 5.3.5.2-2, Study 531-002) |
| Hb | Hemoglobin |
| HLA | Human leukocyte antigen |
| ICH | International council for harmonization of technical requirements for pharmaceuticals for human use |
| IgG | Immunoglobulin G |
| ITP | Idiopathic thrombocytopenic purpura |
| LDH | Lactate dehydrogenase |
| MDS | Myelodysplastic syndrome |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PBRER | Periodic benefit-risk evaluation report |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PNH | Paroxysmal nocturnal hemoglobinuria |
| PPS | Per protocol set |
| PSUR | Periodic safety update report |
| PT | Preferred term in MedDRA |
| Reference Guideline for Clinical Practice on AA, revised version 2014 | Reference Guideline for Clinical Practice on Aplastic Anemia, revised version 2014 (revised on February 22, 2015, Research Group for Idiopathic Hematopoietic Disorder, the Policy Research Project for Intractable Diseases funded by the Health, Labour and Welfare Sciences Research Grants) |
| Reference Guideline for Clinical Practice on AA 2018 | Reference Guideline for Clinical Practice on Aplastic Anemia, revised version 2018 (revised on May 13, 2018, Research Group for Idiopathic Hematopoietic Disorder, the Policy Research Project for Intractable Diseases funded by the Health, Labour and Welfare Sciences Research Grants) |
| Romiplate | Romiplate for S.C. Injection 250 μg |
| Romiplostim | Romiplostim (Genetical Recombination) |
| SMQ | Standardized MedDRA Query in MedDRA |
| $t_{max}$ | Time to reach maximum concentration |
| TPO | Thrombopoietin |