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ORIGINAL ARTICLE

Romiplostim for the treatment of chronic immune thrombocytopenia in adult Japanese patients: a double-blind, randomized Phase III clinical trial

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Abstract The efficacy and safety of romiplostim, a thrombopoietin-mimetic peptibody, were evaluated in a double-blind, placebo-controlled, randomized trial of Japanese patients with chronic immune thrombocytopenia (ITP). Thirty-four ITP patients received romiplostim ($n = 22$) or placebo ($n = 12$) for 12 weeks, with a starting romiplostim dose of 3 μg/kg weekly. The primary end point was the number of weeks with platelet response, defined as a platelet count $\geq 50 \times 10^9$/L (not including the 4 weeks after rescue medication administration). Patients received a median of 4 (range 1–19) prior ITP therapies including splenectomy in 44%. On study, 68% also received concomitant ITP therapy. Weekly responses occurred for a median of 11 weeks with romiplostim as compared to 0 weeks with placebo ($p < 0.0001$). Most romiplostim-treated patients (95%) achieved platelet responses; two showed extended responses after the treatment period. The use of rescue medication was required in

The work was done at multiple clinical investigational sites within Japan.

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9% of romiplostim-treated patients as compared with 17% of placebo-treated patients. Both treatment groups had similar incidences of adverse events (91% romiplostim, 92% placebo). Adverse events that occurred more frequently (>10%) in romiplostim-treated patients included nasopharyngitis, headache, peripheral edema, back pain, and extremity pain. In conclusion, romiplostim significantly increased and maintained platelet counts and was well tolerated in Japanese patients with ITP.

Keywords Idiopathic thrombocytopenic purpura · TPO-receptor agonist · Japan · Efficacy · Safety

1 Introduction

Immune thrombocytopenia (ITP) is an immune-mediated disorder characterized by low peripheral platelet counts (i.e., $<100 \times 10^9$/L) due to both increased platelet destruction and impaired platelet production [1–8]. A diagnosis of primary ITP is made based on history, complete blood counts, and exclusion of potential underlying causes [9]. ITP in adults generally appears in a chronic form, with the definition of chronic ranging from ITP of at least 6 months duration to at least 12 months duration [7, 9–12]. Causal factors may include active *Helicobacter pylori* infection; *H. pylori* eradication therapy appears to improve thrombocytopenia in some ITP patients [13–18]. ITP appears to be more frequent in women, particularly between the ages of 30–60 years [10, 11, 19, 20]. Recent reports of incidence rates range from 1.6 to 3.9 per 100,000 person-years in Northern European populations [10, 19, 20], and both incidence and prevalence of chronic ITP increase with age [10, 19, 20]. The incidence and prevalence of ITP in Japan is similar to that observed in other countries, with approximately 70% of cases occurring in patients older than 50 years [15, 21].

As the clinical presentation of ITP varies considerably, the management of chronic ITP is best tailored to the individual patient [5, 9]. In Japan, *H. pylori* eradication therapy is recommended as first-line therapy for *H. pylori*-positive ITP patients [15]. Treatments for ITP are only clearly indicated for those patients with an extremely low platelet count ($<10 \times 10^9$/L) and/or with severe bleeding symptoms [22]. Treatment is not recommended for patients with platelet counts $>50 \times 10^9$/L in the absence of bleeding, trauma/surgery, or other risk factors [11]. Available treatment options include corticosteroids and other immunosuppressive agents, splenectomy, and immunoglobulins [6, 11, 23]. Approximately, 20–35% of ITP patients have disease refractory to treatment with steroids, immunoglobulins, or splenectomy [22, 24], and only two-thirds of patients undergoing splenectomy experience sustained response without additional therapy [11]. As not all patients respond to these treatment options, which are often associated with various side effects [22], additional safe and effective management strategies are needed.

Most current therapies aim to reduce platelet destruction. Treatments aimed at increasing thrombopoiesis, such as the thrombopoietin (TPO)-receptor agonists romiplostim and eltrombopag, offer a potentially complementary treatment strategy for ITP [25, 26]. These second-generation thrombopoietic agents are recommended for chronic ITP in patients failing initial therapy with steroids/immunoglobulins or relapse after splenectomy [11]. Romiplostim is a subcutaneously administered F_c-peptide fusion protein composed of 2 identical peptide subunits that activate the TPO receptor, thus leading to an increase in megakaryopoiesis [27]. In studies outside of Japan, romiplostim was shown to be effective for the treatment of chronic ITP with good tolerability. Romiplostim is approved in the USA for the treatment of chronic ITP that has not responded to corticosteroids, immunoglobulins, or splenectomy, and in Europe for the treatment of splenectomized patients with chronic ITP refractory to other treatments or in non-splenectomized patients in whom splenectomy is contraindicated [27]. As of January 2011, romiplostim was approved by the Japanese regulatory authority Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of chronic ITP [28].

Racial groups may differ in terms of disease presentation, adverse-event profiles, drug metabolism, and response to treatment [29, 30]. The potential for clinically relevant efficacy and safety differences between Japanese and Western populations treated with romiplostim thus required assessment. Romiplostim was previously assessed in phase 1 and 2 dose-escalation studies in Japanese patients with ITP. In these studies, romiplostim was found to be safe, well tolerated, and effective at increasing platelet counts in a dose-dependent manner [31, 32]. Results were generally consistent with those from studies on non-Japanese patients. Data from phase 2 studies suggested a romiplostim starting dose of 3 μg/kg in Japanese patients. To further investigate the use of romiplostim in this setting, we conducted a randomized, blinded, phase 3 trial evaluating the efficacy and safety of romiplostim (starting dose of 3 μg/kg) compared with placebo as second-line therapy for chronic ITP in adult Japanese patients.

2 Materials and methods

2.1 Study design and patients

This was a randomized, placebo-controlled, double-blind phase 3 study, similar in design to previous global

romiplostim trials [33, 34]. The study was conducted between 20 November 2007 and 13 April 2009 and enrolled ITP patients from 11 study centers in Japan. The trial adhered to Japanese Ministry of Health, Labour and Welfare regulations, and International Conference on Harmonisation Good Clinical Practice guidelines. Furthermore, the study protocol was approved by all relevant institutional review boards/ethics committees, and patients were required to provide written informed consent prior to entering the trial. The study was registered with http://clinicaltrials.gov under study number NCT00603642.

During the 3-week screening phase and the remainder of the study, platelet counts were assessed every 7 days. Eligibility criteria consisted of: ITP diagnosed at least 6 months before the initial screening visit, $\geq$1 previous treatment for ITP, the mean of 3 scheduled platelet counts (i.e., at weeks -3, -2, and -1 prior to study entry) had to be $\leq 30 \times 10^9$/L (with no individual count $>35 \times 10^9$/L), Japanese race, age $\geq$20 years, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. If patients were found to be *H. pylori* positive, they had to have completed at least 1 course of *H. pylori* eradication therapy at least 12 weeks before the first screening visit. Furthermore, patients were required to have a hemoglobin value of $\geq$10 g/dL, a serum creatinine concentration of $\leq$2 mg/dL, and either total bilirubin $\leq$1.5 times the upper limit of normal (ULN) or alanine aminotransferase and aspartate aminotransferase $\leq$3 times ULN. Patients who received concomitant treatment with oral corticosteroids, azathioprine, and/or danazol administered at constant dose and schedule from at least 4 weeks prior to the first screening visit were permitted into the study. However, patients who had received any other drug (including immunoglobulins) to increase platelet counts within 2 weeks before screening were excluded, as were those who received hematopoietic growth factors, anti-malignancy agents, or any monoclonal antibodies within 4, 8, or 14 weeks of screening, respectively. Other key exclusion criteria included: splenectomy within 12 weeks before the first screening visit, history of bone marrow stem cell disorder or abnormal bone marrow findings (other than those typical of ITP), any active malignancy, arterial thrombosis, and a history of venous thrombosis necessitating anticoagulation therapy.

2.2 Interventions

Romiplostim was provided by the study sponsor in 5-mL glass vials as a sterile, white, lyophilized powder containing a protein concentration of 0.5 mg/mL in 10 mM histidine, 4% mannitol, 2% sucrose, and 0.004% polysorbate 20, at pH 5 when reconstituted with 1.2 mL of sterile water. Placebo was supplied in identical vials.

After the initial screening period, eligible patients were randomized to either romiplostim or placebo in a 2:1 ratio stratified by splenectomy status. The randomization procedure was conducted centrally by Transcosmos Inc. (Tokyo, Japan) using a pre-prepared randomization list and communication via fax. Treatment was administered in a blinded fashion as a subcutaneous injection on the same day as the assessment of weekly platelet response and was continued for a total of 12 weeks, with a starting dose of 3 μg/kg once weekly. Dose adjustment was permitted up to a maximum of 10 μg/kg once weekly to achieve a platelet count within the target range of $\geq$50 to $\leq 200 \times 10^9$/L. The dose was increased or decreased by 1 μg/kg after 2 consecutive weeks of platelet counts within a range of $\geq$10 to $<50 \times 10^9$/L or >200 to $\leq 400 \times 10^9$/L, respectively. For these patients, the dosage could be increased or decreased every 2 weeks. For patients with platelet counts of $<10 \times 10^9$/L, dosages were to be increased by 1 μg/kg every week. For platelet counts over 400×10^9/L, the romiplostim dose was held until platelet counts were under 400×10^9/L, after which the dose was decreased by 1 μg/kg every week. If a dosage reduction was required at a dose of 1 μg/kg, treatment administration was to be withheld until platelet count fell to $<50 \times 10^9$/L.

Throughout the study, rescue medication was permitted for severe bleeding or if the investigator believed that the patient was at immediate risk of bleeding. Rescue medication was defined as any medication administered for the intended purpose of raising platelet counts; permitted were intravenous immunoglobulin, platelet transfusions, corticosteroids, and an increase in dose or frequency of a concomitant oral corticosteroid, azathioprine, and/or danazol. Patients who required rescue medications during the treatment period were to continue receiving randomized therapy. After cessation of treatment following 12 weeks of therapy, patients' weekly platelet counts were monitored for an additional 12 weeks or until their platelet count dropped to $\leq 50 \times 10^9$/L, whichever occurred first.

2.3 Study end points

All end points were defined prospectively and were assessed in the full analysis set, i.e., all patients who received at least one dose of the investigational product. The primary efficacy end point was the number of weeks with platelet response, i.e., a platelet count of $\geq 50 \times 10^9$/L; platelet counts within 4 weeks following rescue medication use were not included as responses. Secondary end points included the proportion of patients with an increase of platelet count $\geq 20 \times 10^9$/L from baseline, the change from baseline in the mean of the last 4 platelet counts during weeks 2–13, the number of weeks with platelet

counts in the target range of ≥50 to ≤200 × 10^9/L during weeks 2–13, and the incidence of rescue medication use.

Assessment of bleeding symptoms, physical examination, vital sign assessment, hematology and blood chemistry tests, and recording of adverse events were performed at regular intervals throughout the study. The presence of romiplostim and TPO antibodies was assessed from blood samples obtained at week 1 pre-dose and at the end-of-treatment visit (i.e., 1 week after the scheduled visit for the last administration of the investigational product), using a previously described method [35].

2.4 Statistical analysis

Approximately, 30 patients were planned for randomization. This sample size was conservatively estimated to provide ≥90% power for a comparison of the primary end point between treatment arms using a Wilcoxon rank sum test at a 2-sided significance level of 0.05. Proportions of patients with an increase of platelet count ≥20 × 10^9/L from baseline and with rescue medication use were compared by Fisher's exact test. The changes from baseline in the mean of the last 4 platelet counts were compared by analysis of covariance using baseline platelet count as a covariate. Other prospectively planned analyses were summary statistics exploring the influence of splenectomy status and concomitant ITP therapy on the primary and secondary end points, as well as assessing median times to first platelet count of <50 × 10^9/L or the need for rescue medication after treatment cessation using a Kaplan–Meier estimate; the respective 95% CI was calculated using the Brookmeyer and Crowley method [36].

3 Results

3.1 Patient characteristics

A total of 34 patients were eligible for inclusion into the study, of which 22 were randomized to romiplostim and 12 to placebo. All participants completed the study through week 12 (Fig. 1). All patients had previously received corticosteroids for prior ITP treatment. Among the overall study population, patients had received a median of 4 (1–19) prior ITP therapies, 15 patients (44.1%) had previously undergone a splenectomy, and 23 (67.6%) were receiving concomitant ITP therapy at baseline. Of note, twice as many patients in the romiplostim group had undergone prior *H. pylori* eradication therapy. More patients in the placebo group were female and receiving concomitant ITP therapy. Otherwise, both groups were well matched for baseline demographics and clinical characteristics, including baseline platelet counts (Table 1).

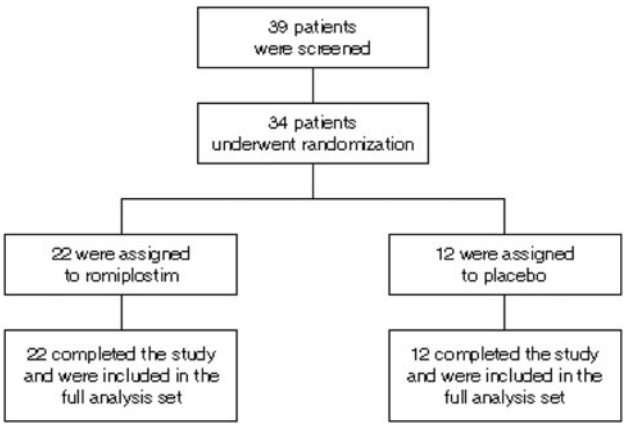

Fig. 1 Patient disposition throughout the study

The mean treatment duration was 12.0 (±0.1) weeks in the romiplostim group and 11.9 (±0.3) weeks in the placebo group. The dose for the romiplostim group increased slightly from the protocol-specified starting dose of 3 μg/kg to a mean of 3.2 μg/kg at week 2 and then decreased to a range of 2.1–2.8 μg/kg from weeks 3 to 12, whereas the mean virtual dose for the placebo group increased steadily throughout the study to a maximum of 8.7 μg/kg at week 11 (Fig. 2). Doses of romiplostim were comparable regardless of splenectomy and concomitant ITP therapy status.

3.2 Efficacy

Romiplostim was superior ($p < 0.0001$) to placebo in the primary end point of weeks of response, with a median duration of platelet response (lower quartile, upper quartile) of 11 weeks (9, 12) in the romiplostim group and 0 weeks (0, 0) in the placebo group. In patients treated with romiplostim, results were similar in splenectomized and non-splenectomized patients (median 11.0 vs. 10.5 weeks) and in patients with or without concomitant ITP therapy at baseline (median 11.0 vs. 10.0 weeks). Platelet responses could be observed in the romiplostim group as early as 1 week after the first administration of the study drug, and the response rate remained stable throughout the treatment period (Fig. 3a). Of note, splenectomy status did not appear to have an effect on weekly platelet response in either treatment arm (Fig. 3b). After week 7, treatment response appeared to be slightly better in romiplostim-treated patients administered concomitant ITP therapy ($n = 13$) than in patients who received romiplostim only ($n = 9$); however, the patient numbers in each of these subpopulations were relatively small, so this apparent difference may be due to random variation in the sample rather than a true treatment effect (Fig. 3c). The mean romiplostim dose immediately prior to the first weekly platelet response was 3.2 (±0.4) μg/kg regardless of splenectomy status and

Table 1 Patient demographics and baseline characteristics

Patient baseline characteristic	Romiplostim ($N = 22$)	Placebo ($N = 12$)
Gender, *n* (%)		
Female	14 (63.6%)	10 (83.3%)
Male	8 (36.4%)	2 (16.7%)
Age, mean (SD)	58.5 (±12.6) years	47.6 (±13.4) years
Race, *n* (%)		
Japanese	22 (100%)	12 (100%)
Weight, mean (SD)	58.3 (±11.4) kg	58.2 (±12.6) kg
ECOG performance status, *n* (%)		
0	17 (77.3%)	11 (91.7%)
1	5 (22.7%)	1 (8.3%)
Time since ITP diagnosis, mean (SD)	9.7 (±10.4) years	7.6 (±5.9) years
Platelet count, mean (SD)	18.4 (±8.3) $\times 10^9$/L	15.8 (±.6) $\times 10^9$/L
Concomitant ITP therapy, *n* (%)		
Yes	13 (59.1%)	10 (83.3%)
No	9 (40.9%)	2 (16.7%)
Splenectomy status		
Yes, *n* (%)	10 (45.5%)	5 (41.7%)
No, *n* (%)	12 (54.5%)	7 (58.3%)
Time since splenectomy, mean (SD)	8.1 (±6.8) years	10.6 (±6.9) years
Number of prior ITP treatments, median (range)	4 (1, 19)	4 (1, 7)
ITP treatment history, *n* (%)		
Corticosteroid	22 (100.0%)	12 (100.0%)
IV immunoglobulin	11 (50.0%)	8 (66.7%)
H. pylori eradication therapy	11 (50.0%)	3 (25.0%)
Azathioprine	5 (22.7%)	4 (33.3%)
Danazol	3 (13.6%)	2 (16.7%)
Cyclophosphamide	4 (18.2%)	0 (0.0%)
Rituximab	3 (13.6%)	0 (0.0%)
Vincristine/vinblastine	2 (9.1%)	0 (0.0%)
Other	10 (45.5%)	7 (58.3%)

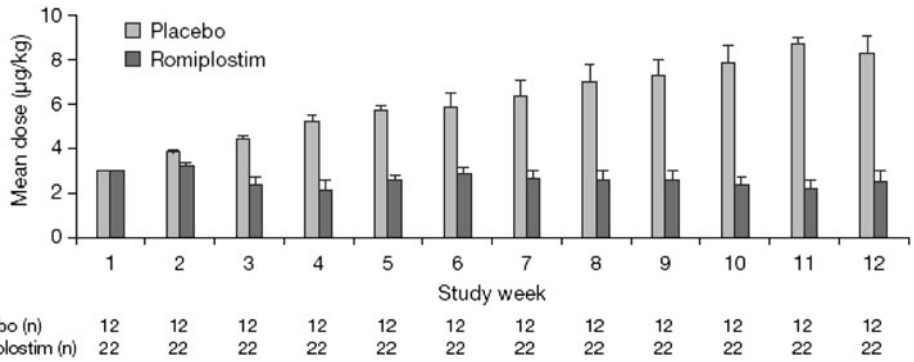

Fig. 2 Mean (+standard error) weekly doses of romiplostim or placebo and number of patients evaluated at each time point

concomitant ITP treatment. To address the concern that the imbalance in prior *H. pylori* eradication therapy between the 2 treatment groups may have influenced the observed treatment difference, a post-hoc analysis of platelet response stratified by *H. pylori* status was conducted. After stratification according to prior *H. pylori* eradication therapy, romiplostim remained superior to placebo ($p < 0.0001$).

Romiplostim was also superior to placebo in all secondary efficacy end points, except the proportion of patients requiring rescue medications, the difference of

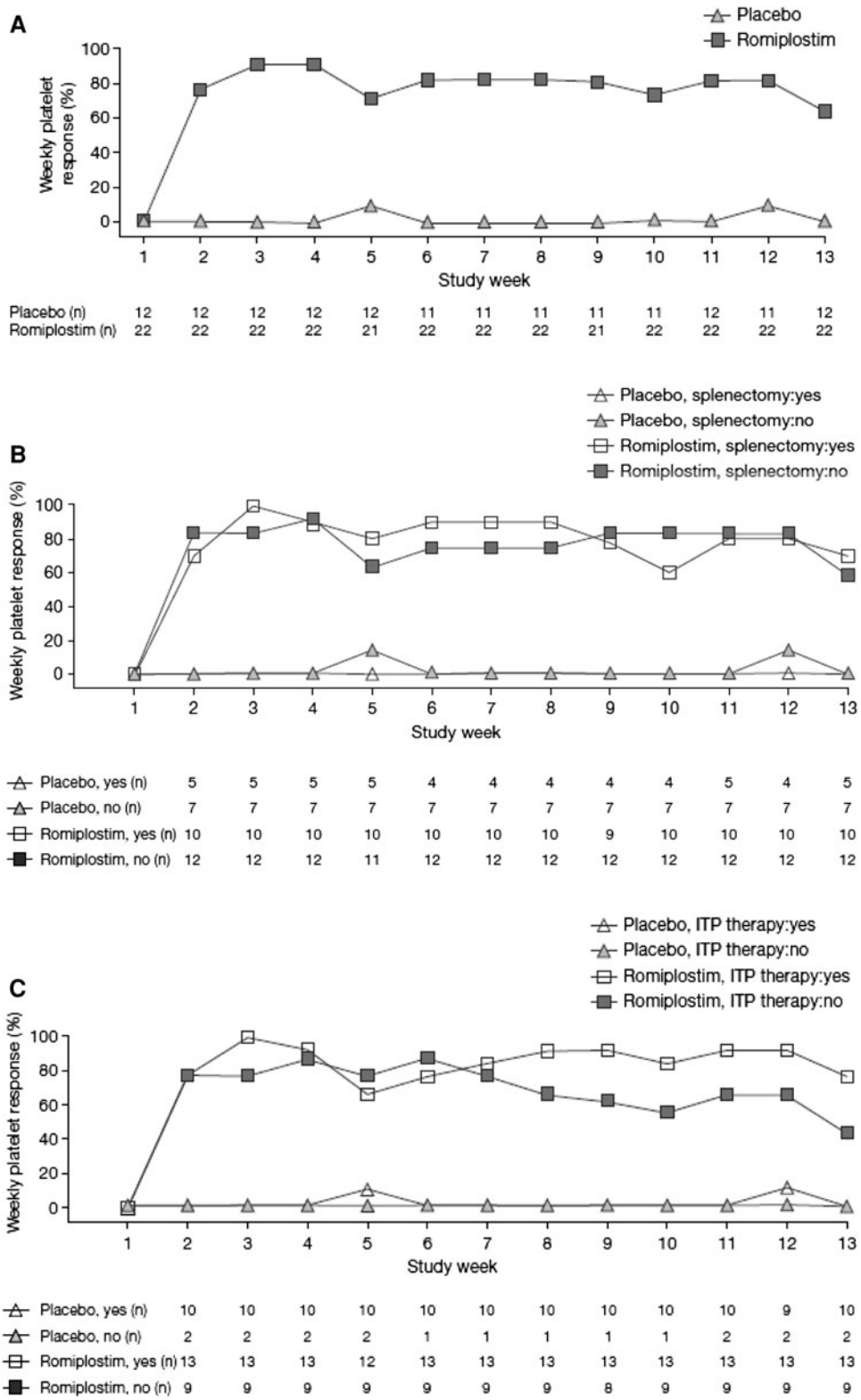

Fig. 3 Weekly platelet response in patients treated with romiplostim or placebo (**a**) and by splenectomy status (**b**) as well as baseline concomitant ITP therapy (**c**)

which was not statistically significant. Detailed results and comparisons for all efficacy end points are listed in Table 2. The mean weekly platelet count was significantly higher for patients given romiplostim than those receiving placebo at all times (Fig. 4). The number of patients whose highest platelet count was $\geq 50 \times 10^9$/L and had doubled from baseline was 21/22 (95.5%) in the romiplostim group and 1/12 (8.3%) in the placebo group. After cessation of

Table 2 Primary and secondary efficacy outcomes in patients treated with romiplostim or placebo

	Romiplostim ($N = 22$)	Placebo ($N = 12$)	p value
Primary end point			
Weekly platelet response: platelet count of $\geq 50 \times 10^9$/L, median (Q1, Q3)	11.0 (9, 12) weeks	0.0 (0, 0) weeks	<0.0001
Secondary end points			
Proportion of patients with increase of platelet count $\geq 20 \times 10^9$/L from baseline, incidence rate, n (%)	21 (96%)	3 (25%)	<0.0001
Change from baseline in mean of last 4 platelet counts during weeks 2–13, mean (SD)	110 (89) $\times 10^9$/L	2 (7) $\times 10^9$/L	0.0003
Number of weeks with platelet counts in target range of ≥ 50 to $\leq 200 \times 10^9$/L, median (Q1, Q3)	7 (3, 9) weeks	0 (0, 0) weeks	<0.0001
Proportion of patients requiring rescue medications, incidence rate, n (%)	2 (9%)	2 (17%)	0.6015

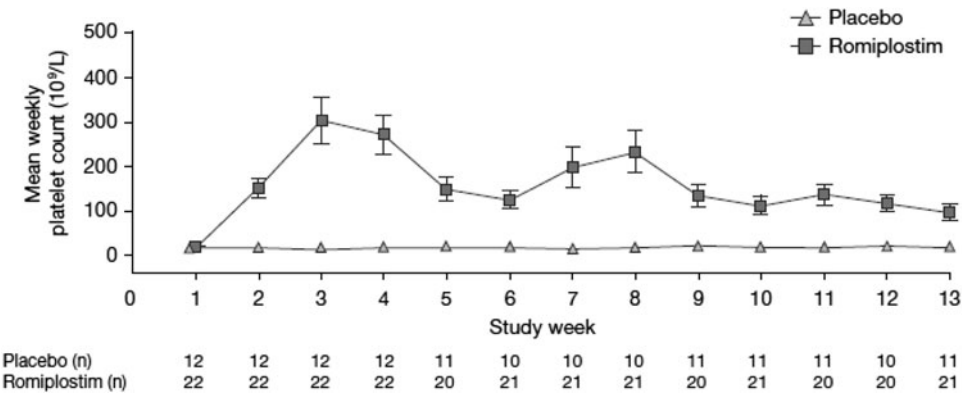

Fig. 4 Mean (±standard error) weekly platelet count and number of patients evaluated at each time point

romiplostim treatment (i.e., from week 13 onwards), the median time to a first platelet count of $<50 \times 10^9$/L or to receiving rescue medication was 1.0 weeks (95% CI 1.0, 2.0; assessed by Kaplan–Meier method). Of note, among romiplostim-treated patients, platelet counts after the 12-week treatment period remained above 50×10^9/L for 8 weeks in one study participant and for 12 weeks in another. Only 1 patient treated with romiplostim did not achieve a treatment response. This patient exhibited severe thrombocytopenia at baseline (5×10^9/L) and platelet count increased during the course of romiplostim therapy to a maximum of 19×10^9/L (week 11). Furthermore, this patient had bleeding symptoms (i.e., purpura/petechiae and oral bleeding) present at baseline, which resolved after initiation of romiplostim therapy and did not recur throughout the study.

An improvement in the occurrence of bleeding symptoms (i.e., purpura/petechiae, epistaxis, oral bleeding, menorrhagia, bruising, intracranial bleeding, gastrointestinal bleeding, and/or other bleeding symptoms) was observed in romiplostim-treated patients, including after the 12-week treatment period. The incidence of any of these bleeding symptoms in the placebo group was 83.3% at baseline and week 5, 100% at week 9, and 83.3% at week 13. Romiplostim decreased the incidence of bleeding symptoms from 63.6% at baseline to 31.8% at weeks 5 and 9, and 36.4% at week 13. During the 12-week follow-up period, 100% of placebo and 72.7% of romiplostim patients had bleeding symptoms.

3.3 Safety

Similar proportions of patients in both treatment groups (91.7% placebo, 90.9% romiplostim) experienced adverse events from any cause. Incidences of serious adverse events (8.3% placebo, 9.1% romiplostim) and adverse events that were graded 3 (severe) in severity (8.3% placebo, 9.1% romiplostim) were also similar. Adverse events that occurred in at least 10% of patients in either treatment group are shown in Table 3. Adverse events that were recorded with >5% higher frequency in the romiplostim group than in the placebo group were nasopharyngitis (41 vs. 17%), headache (32 vs. 17%), peripheral edema (18 vs. 0%), back pain (14 vs. 0%), pain in the extremities (14 vs. 0%), nephrocalcinosis (9 vs. 0%), thermal burn injury (9

Table 3 Adverse events occurring in at least 10% of patients in either treatment group

Adverse event, *n* (%)	Romiplostim ($N = 22$)	Placebo ($N = 12$)
Nasopharyngitis	9 (41%)	2 (17%)
Headache	7 (32%)	2 (17%)
Peripheral edema	4 (18%)	0 (0%)
Back pain	3 (14%)	0 (0%)
Pain in extremity	3 (14%)	0 (0%)
Malaise	1 (5%)	2 (17%)
Contusion	0 (0%)	2 (17%)

vs. 0%), thrombocytopenia (9 vs. 0%), and fatigue (9 vs. 0%). Most of these events had resolved by the end of the study, except for 2 events of back pain, all 2 events of nephrocalcinosis, 2 events of thrombocytopenia, and 1 event of fatigue. In the romiplostim group, 3 events of thrombocytopenia occurred after cessation of dosing: 1 in an 81 year-old female, first observed on day 92, ongoing at the study end, and not judged as treatment related, and 2 out of 3 observed in a 78 year-old male, in whom the final event of thrombocytopenia also occurred on day 92, remained ongoing at the study end, was not judged as treatment related, and was judged as serious. In both of these patients, platelet counts fell below those recorded at baseline. Significant (≥grade 3) bleeding events occurred in 1 patient in the romiplostim group (subarachnoid hemorrhage during week 3; week 3 platelet count was 120×10^9/L) and 1 patient in the placebo group (subarachnoid hemorrhage, cerebral hemorrhage, and gastrointestinal hemorrhage during week 10; no platelet measure taken that week, but week 11 platelet count was 23×10^9/L). There were no adverse events of bone marrow reticulin or thrombosis, and no detection of neutralizing antibodies to romiplostim or TPO.

Adverse events considered to be treatment related by the investigator also occurred in similar proportions of patients in the two treatment groups (33.3% placebo, 40.9% romiplostim); no serious treatment-related adverse events were reported. Three treatment-related adverse events were observed with a >5% higher frequency in the romiplostim group than in the placebo group. These were headache (23 vs. 8%), fatigue (9 vs. 0%), and pain in extremity (9 vs. 0%). All treatment-related events were considered mild in severity and no treatment-related event was serious. Two patients (9%) in the romiplostim group reported a total of 2 serious adverse events (thrombocytopenia and subarachnoid hemorrhage), and 1 patient (8%) in the placebo group reported a total of 3 serious adverse events (gastrointestinal hemorrhage, cerebral hemorrhage, and subarachnoid hemorrhage). Of note, no thrombotic or thromboembolic events were reported in this study. One subject in the placebo group discontinued investigational product temporarily due to moderate depression. No patients died during the study, within 30 days after the end of the treatment phase, or at the end of the study, and none withdrew from the study due to an adverse event or for any other reason.

4 Discussion

In this randomized, blinded, phase 3 trial, romiplostim at a starting dose of 3 μg/kg significantly increased and maintained platelet counts and was well tolerated in Japanese patients with ITP. This study was similar in design to previous key romiplostim trials, but with a shorter treatment duration and a somewhat higher starting dose [34, 37]. Romiplostim was superior to placebo in the primary and most secondary efficacy end points. The only secondary end point that was not statistically different between treatment groups was the use of rescue medication, which was relatively low compared to previous trials with the TPO-receptor agonists [34, 38]. Conversely, administration of concomitant ITP therapy was more than twice as high as in other phase 3 studies of romiplostim [34], and was more frequent in the placebo group. In Japan, the administration of rescue medication is typically only considered for patients with clinically important bleeding episodes (e.g., oral or severe bleeding; or those with severe thrombocytopenia [1]), while this study tended to enroll clinically stable patients with chronic ITP. Only one patient in the romiplostim arm was judged as a non-responder; of note, this individual had severe baseline thrombocytopenia and romiplostim did provide some clinical benefit (i.e., a slight increase in platelet counts and resolution of bleeding symptoms) over the course of the study period.

The safety profile of romiplostim in Japanese patients was also consistent with that seen in non-Japanese populations. There were no deaths during the course of the study, no treatment discontinuation with romiplostim, and no signs that neutralizing antibodies to either TPO or romiplostim had developed in any of the study participants. While bone marrow reticulin has been detected in some patients receiving TPO-receptor agonists [39–41], this was not observed among patients in this study. Some patients experienced thrombocytopenia after cessation of romiplostim administration; worsening thrombocytopenia is a known risk after discontinuation of therapy with romiplostim and TPO-receptor agonists in general [11]. No clinically important safety concerns were identified. Of note, the great majority of patients in this study had a clinically significant response to romiplostim as second-line ITP therapy. Furthermore, response to romiplostim appears to compare well to that achieved with other second-line therapy options, which have widely varying (10–85%) but

generally low response rates. There is currently no preference for a particular second-line therapy in this setting [1, 11]. Based on these overall observations, romiplostim appears to be a potentially useful treatment option in Japanese patients with ITP.

Racial groups exhibit potential differences in terms of drug metabolism, disease presentation, treatment response, and adverse-event profiles across a range of different disease types [29, 30]. For instance, a population pharmacokinetic study of the TPO-receptor agonist eltrombopag suggested that this agent should be initiated at lower doses in East-Asian ITP patients [42, 43]. It was therefore of interest to evaluate the efficacy and safety of romiplostim in Japanese patients in a randomized, controlled, phase 3 trial, using a study design similar to phase 3 trials conducted in largely non-Asian patient populations [34], thus allowing for a meaningful comparison between Japanese and non-Japanese patients. This study differed from previous key romiplostim trials only in that there was a shorter treatment duration and a higher starting dose (3 vs. 1 μg/kg) [34, 37]. However, the recent randomized phase 3 trial demonstrating superiority of romiplostim over standard of care in the treatment of chronic ITP in non-splenectomized patients used the same dose range as in this study [40]. In our study, treatment with an initial dose of 3 μg/kg yielded a very rapid therapeutic response in about 80% of patients from week 2 onwards. In comparison, past studies with a starting dose of 1 μg/kg, resulted in somewhat slower attainment of response, i.e., approximately 50% of patients in the same timeframe [34]. Although no safety concerns (e.g., thrombotic events caused by the increase in platelet counts) were identified with the higher starting dose, platelet counts should be closely monitored and the romiplostim dose modified until stable, adequate platelet counts have been achieved.

This study was somewhat limited by its relatively short duration (i.e., a 12-week treatment period and 12-week follow-up period) and the small number of participants. The relatively small sample size, especially of the subpopulations, should be considered when evaluating the study results. For instance, random variation rather than a true treatment effect may have contributed to the slight differences observed (about half-way through the trial) in platelet responses among patients treated with romiplostim only as compared with those who received additional concomitant ITP therapy. Inclusion criteria specified that ITP be diagnosed at least 6 months prior to study entry, as per the definition of chronic ITP generally accepted at the time the trial was designed. This is shorter than the currently accepted definition of chronic ITP, which requires the disorder to have been present for a year before a diagnosis of chronic disease is made [7]. However, the long mean time since ITP diagnosis observed in both treatment groups confirms that we studied a patient population consistent with the current definitions of chronic adult ITP. The results of this phase 3 trial clearly suggest a clinical benefit of romiplostim for the second-line treatment of chronic ITP in Japanese patients, in a patient population that closely reflects that treated for refractory ITP in clinical practice. While the study duration was sufficient to evaluate the efficacy and safety of romiplostim in a Japanese population, future investigations should continue to assess the long-term use of romiplostim in this setting.

In conclusion, romiplostim was an effective, safe, and well-tolerated agent for the treatment of ITP in Japanese patients; The efficacy and safety results were largely consistent with those previously obtained in a non-Japanese patient population. The results of this study lend further support to current clinical guidelines [11] that include romiplostim as a second-line therapy option for the treatment of chronic ITP in patients with insufficient response to other treatments.

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Conflict of interest Y.T. received speaker's honoraria from Kyowa Hakko Kirin Co. and GlaxoSmithKline; M.K. is a consultant to Novartis and Shionogi & Co., Ltd.; H.W. and R.L. are stockholders and employees of Amgen Inc. The remaining authors have no relevant conflicts of interest to report.

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