Int J Hematol (2009) 90:157–165
DOI 10.1007/s12185-009-0361-y

ORIGINAL ARTICLE

# A phase II, open-label, sequential-cohort, dose-escalation study of romiplostim in Japanese patients with chronic immune thrombocytopenic purpura

**Yukari Shirasugi · Kiyoshi Ando · Satoshi Hashino · Toshiro Nagasawa · Yoshiyuki Kurata · Yuji Kishimoto · Koji Iwato · Tomoko Ohtsu · Dietmar P. Berger**

Received: 16 March 2009 / Revised: 4 May 2009 / Accepted: 25 May 2009 / Published online: 20 June 2009


**Abstract** This phase II, multicenter, open-label, sequential-cohort, dose-escalation study was designed to evaluate the safety and efficacy of romiplostim, a novel peptibody that increases platelet production, in Japanese patients with chronic immune thrombocytopenic purpura (ITP). Sequential cohorts of four patients each received romiplostim (1, 3, or 6 μg/kg) subcutaneously on days 1 and 8 of the dose-escalation phase. Patients who achieved platelet responses (doubling of baseline platelet counts to $\geq 50 \times 10^9$/L) continued romiplostim weekly during the treatment-continuation phase. Romiplostim produced dose-dependent increases in mean and peak platelet counts. Five patients received romiplostim during the treatment-continuation phase, with platelet counts $\geq 50 \times 10^9$/L maintained in approximately half of the weekly assessments. Romiplostim was well tolerated. No severe, serious, or life-threatening adverse events were reported. No binding antibodies to romiplostim or thrombopoietin were detected. Romiplostim is safe and well tolerated in Japanese patients with chronic ITP and is effective in producing platelet count increases, consistent with the results from studies in non-Japanese patients. On the basis of these findings, a starting dose of 3 μg/kg was recommended for phase III evaluation of romiplostim in Japanese patients with chronic ITP.

**Keywords** Immune thrombocytopenic purpura · Romiplostim · Thrombopoiesis · Platelet production

Y. Shirasugi · K. Ando
Tokai University Hospital, Isehara, Japan

S. Hashino
Hokkaido University Hospital, Sapporo, Japan

T. Nagasawa
Tsukuba University Hospital, Tsukuba, Japan

Y. Kurata
Osaka University Hospital, Suita, Japan

Y. Kishimoto
Kansai Medical University Takii Hospital, Moriguchi, Japan

K. Iwato
Hiroshima Red Cross Hospital and Atomic-Bomb Survivors Hospital, Hiroshima, Japan

T. Ohtsu
Amgen KK, Tokyo, Japan

D. P. Berger (✉)
Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA
e-mail: dberger@amgen.com

## 1 Introduction

Chronic immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by antibody-mediated platelet destruction and suboptimal platelet production [1–4]. Initial therapy typically consists of corticosteroids or intravenous immunoglobulins (IVIg), followed by low-dose corticosteroids (prednisone, 1–2 mg/kg/day) if thrombocytopenia persists. Either repeated administrations of IVIg or splenectomy can be used for intolerance or insufficient response to low-dose corticosteroids [1, 3]. These treatments as well as others used in refractory patients, such as rituximab and cyclophosphamide, suppress the rate of platelet destruction [5–7]. However in many cases they are either transiently effective, insufficiently effective, or poorly tolerated. In addition to the platelet destruction, the rate of platelet production is

inadequate in a majority of patients with chronic ITP [4, 8–11]. Accordingly, treatments that increase platelet production may offer the potential for improved control and outcomes in chronic ITP [12]. Platelet production is primarily regulated by thrombopoietin (TPO), which binds to the TPO receptor (c-Mpl) to increase the megakaryocytopoiesis and thrombopoiesis.

The potential clinical benefit of using a thrombopoietic growth factor to treat chronic ITP was initially demonstrated using pegylated recombinant human megakaryocyte growth and development factor (MGDF), a truncated form of human TPO [13]. Administration of MGDF for 7 days increased platelet counts in 3 of 4 Japanese ITP patients and bleeding was decreased. The production of antibodies against MGDF in healthy volunteers that cross-reacted with endogenous TPO [14] resulted in the discontinuation of MGDF clinical studies and led to the development of novel TPO mimetics. Romiplostim (AMG 531) is an Fc-peptide fusion protein (peptibody) that increases platelet production via the same mechanism as endogenous TPO [15, 16]. However, romiplostim does not share sequence homology with TPO. This lack of sequence homology reduces the probability that antibodies to romiplostim, if produced, would cross-react with endogenous TPO and cause further thrombocytopenia [14]. Initial clinical trials with romiplostim in the United States and Europe showed that romiplostim increases platelet counts in healthy volunteers and during short-term use by patients with chronic ITP [17–19]. Recent phase III studies conducted in the United States and Europe showed that romiplostim raised and sustained platelet counts in splenectomized and non-splenectomized patients with chronic ITP during treatment for 24 weeks [20]. In these studies, platelet responses were defined as durable or transient and required that rescue medication had not been administered in the preceding 8 weeks. Durable platelet responses, a very rigorous end point that required platelet counts $\geq 50 \times 10^9$/L for at least 6 of the last 8 weeks of treatment without a need for rescue medication, were achieved significantly more often with romiplostim than with placebo in splenectomized patients (38 vs. 0%; $P = 0.0013$) and non-splenectomized patients (61 vs. 5%; $P < 0.001$). The overall platelet response rate (i.e., either transient or durable responses with platelet counts $\geq 50 \times 10^9$/L for 4 weeks or more) was also significantly higher with romiplostim than placebo in splenectomized patients (79 vs. 0%; $P < 0.0001$) and non-splenectomized patients (88 vs. 14%; $P < 0.0001$). Romiplostim treatment also allowed many patients to reduce or discontinue concomitant ITP therapies and was well tolerated in each of the phase II and III trials in Western countries.

The incidence of chronic ITP in adults in Japan is estimated to be 500–2000 cases annually, a rate of incidence similar to that seen in Western countries [1, 21, 22]. The safety, pharmacodynamics, and pharmacokinetics of romiplostim in Japanese adult patients were demonstrated in a phase I study and were consistent with those seen previously in healthy non-Japanese subjects [21]. In the phase I Japanese study, romiplostim increased platelet counts in a dose-related manner, with four of eight patients who received a dose of 1 μg/kg and seven of eight patients who received a dose of 2 μg/kg having platelet increases $\geq 1.5$ times above baseline. The present phase II study was conducted to evaluate the safety and tolerability of romiplostim and its effect on platelet counts in Japanese patients with chronic ITP, and to identify an appropriate starting dose for a phase III study of romiplostim for the treatment of chronic ITP in adult Japanese patients.

## 2 Methods

### 2.1 Study design

This phase II, open-label, sequential-cohort, dose-escalation study was conducted at six centers in Japan and consisted of a 3-week screening period, a 2-week dose-escalation phase and subsequent treatment-continuation phase, and a 3-week follow-up observation period (Fig. 1). It was conducted in accordance with the principles of the Japanese Ministry of Health, Labor and Welfare and International Conference on Harmonization guidelines of Good Clinical Practice. The study protocol and informed consent form were approved by the institutional review board at each study site before any patients were enrolled.

Patients were screened for eligibility over a 3-week period, during which platelet counts were determined each week (days −21, −14, and −7). The baseline platelet count necessary for enrollment was based on the mean of these determinations. Physical examination, vital signs, and laboratory testing were performed at one visit during the screening period. In addition, bone marrow testing was done in all patients aged over 60 years who had not had such testing within the previous 5 years. For the dose-escalation phase, four patients were to be enrolled at each of four sequential dose levels of romiplostim (1, 3, 6, 10 μg/kg). Each dose was administered subcutaneously once weekly for 2 weeks (i.e., days 1 and 8), with no dose adjustments allowed. According to the study protocol, the dose-escalation phase was to be stopped if at least three subjects in a cohort had platelet counts $>450 \times 10^9$/L; at least two subjects in a cohort had platelet counts $>700 \times 10^9$/L; at least one subject in a cohort had platelet counts $>1000 \times 10^9$/L; or if two or more subjects in a cohort had drug-related serious adverse events.

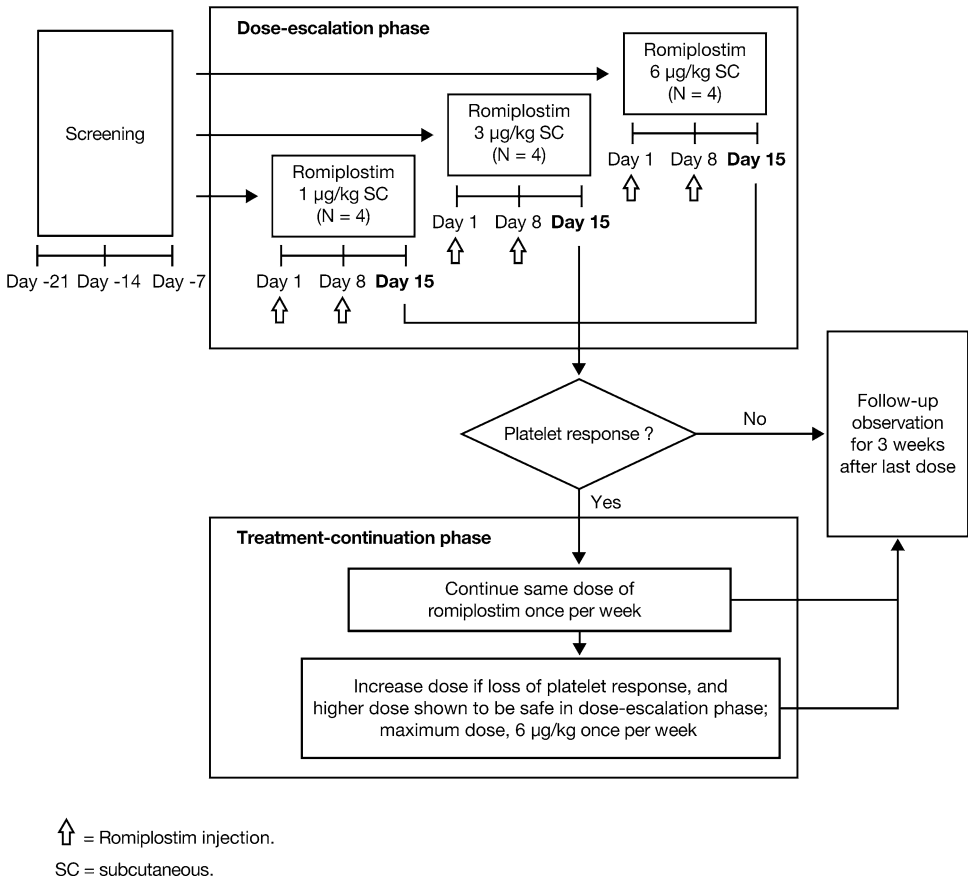


**Fig. 1** Study design

Patients who achieved a platelet response, defined as a doubling of the baseline platelet counts to a level $\geq 50 \times 10^9$/L, during the dose-escalation phase were eligible to continue into the treatment-continuation phase. Patients continued to receive romiplostim once weekly at the original dose, with the option of adjusting the dose to achieve platelet counts in a target range of 50–200 $\times 10^9$/L. The treatment-continuation phase ended when the final cohort of the dose-escalation phase was completed. At this point, patients entered the follow-up observation phase and had their end of study (EOS) visit 3 weeks after receiving their last dose of romiplostim. Patients entered the observation phase when (1) they failed to respond to romiplostim during the dose-escalation phase, (2) they lost their response during the treatment-continuation phase (defined by two consecutive platelet counts dropping to baseline), or (3) the final dose-escalation cohort was completed. At the end of the study, platelet responders and non-responders were eligible to enter an open-label extension study.

Rescue medications were permitted in the study for a tendency for severe bleeding or if the investigator thought the patient was at immediate risk. These medications were to be given with the intended purpose of raising platelet counts and included IVIg, platelet transfusion, corticosteroids, or an increase in dose or frequency of concurrent corticosteroids. Romiplostim was to be continued in patients who received rescue medications.

## 2.2 Patients

Japanese patients aged 20–70 years with a diagnosis of ITP for at least 6 months before the first screening visit were eligible if their mean platelet count measured at the three screening visits was $<30 \times 10^9$/L while not receiving any ITP therapy or $<50 \times 10^9$/L while receiving a stable dose of corticosteroids. Eligible patients had received at least one previous treatment for ITP and had Eastern Cooperative Oncology Group (ECOG) performance status 0–2, adequate renal and hepatic function, and a hemoglobin level $\geq 10$ g/dL. Patients who were positive for antibodies to *Helicobacter pylori* had to complete one course of *H. pylori* eradication therapy at least 12 weeks before the first screening visit. All patients provided written informed consent.

Patients with a known history of a bone marrow stem cell disorder or abnormal bone marrow findings other than ITP were excluded as were those with arterial thrombosis within the past year, history of venous thrombosis who were receiving anticoagulation therapy, uncontrolled

cardiac disease, uncontrolled hypertension with diastolic blood pressure above 100 mmHg, high risk of thromboembolic events, active malignancy, or major surgery within the past 8 weeks. Patients were excluded if they were currently receiving any treatment for ITP except a stable dose of oral corticosteroids, or if they had received IVIg, high-dose corticosteroid pulse therapy, any drug administered to increase platelet counts, or hematopoietic growth factors within 4 weeks before the first screening visit, or had undergone splenectomy within 12 weeks.

### 2.3 Assessments

In the safety assessment, all adverse events observed by the investigator or reported by the patient were recorded, and their severity and relationship to study drug were determined by the investigator. Safety was also assessed by clinical laboratory testing (hematology, clinical chemistry, and coagulation), by the measurement of vital signs and electrocardiogram and by physical examination. In addition, blood samples were collected on day 1, at week 7, and then once every 8 weeks during the treatment-continuation phase, and at the EOS visit to test for induction of serum antibodies. A biosensor immunoassay was used initially to detect antibodies against romiplostim, the biologically active peptide portion of romiplostim or TPO. If a sample tested positive, a cell-based bioassay was to be used to test for the presence of neutralizing antibodies against romiplostim or TPO activity on cell growth.

Efficacy was assessed by measuring platelet counts. Parameters measured included platelet response (as defined above), peak platelet count, time to peak platelet count, absolute change from baseline to peak platelet count, and ratio of the peak platelet count to the baseline platelet count (i.e., fold change from baseline to peak) in each cohort of the dose-escalation phase.

### 2.4 Statistics

The planned sample size was four patients per dose-level cohort. The safety and efficacy analyses included all patients who received at least one dose of romiplostim, and they were conducted separately for the dose-escalation and treatment-continuation phases. The primary end point was the incidence of adverse events, including the presence of antibodies against romiplostim. Adverse events were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA), summarized by severity and relationship to study drug, and evaluated using descriptive statistics. Secondary end points included the proportion of patients achieving a platelet response; proportion of patients with various peak platelet counts (including doubling of baseline counts, absolute counts $\geq 50 \times 10^9$/L, $\geq 100 \times 10^9$/L, and $\geq 450 \times 10^9$/L, and increases $\geq 20 \times 10^9$/L over baseline); and the peak platelet count, time to peak, and absolute and fold change from baseline to peak platelet count in the dose-escalation phase. For the efficacy evaluation, the baseline platelet count was defined as the average of four scheduled determinations (days −21, −14, and −7 during the screening period and day 1 pre-dose). Each efficacy end point was evaluated using descriptive statistics.

## 3 Results

### 3.1 Patient disposition and demographics

Four patients were enrolled at each of the first three dose levels (1, 3, 6 μg/kg). One patient in the 6-μg/kg cohort had an excessively high-platelet count ($980 \times 10^9$/L), and consequently dose escalation to 10 μg/kg in a new cohort of patients was not performed. All 12 patients who were enrolled completed the dose-escalation phase, and five patients entered and completed the treatment-continuation phase (Fig. 2).

The study cohort of 12 patients, all of whom were Japanese per the study protocol, had a mean age of 55.6 years, and included eight females (66.7%) (Table 1). Overall, the mean duration since ITP diagnosis was 10.3 years, and the mean baseline platelet count was $11.8 \times 10^9$/L. All patients had ECOG performance status 0, except for one patient in the 3-μg/kg cohort with a performance status of 1. Eleven patients (91.7%) had a history of purpura/petechiae, and nine patients (75.0%) had a history of epistaxis and oral bleeding. Seven patients (58.3%) received stable corticosteroid therapy concomitantly with study drug, and three patients had previously undergone splenectomy. Prior medications for ITP included corticosteroids (91.7%), IVIg (58%), and danazol (42%).

### 3.2 Dose-escalation phase

The mean platelet count increased with romiplostim dose when measured on days 8, 11, and 15 (Fig. 3). The proportion of patients with platelet responses by day 8, the first time platelet counts were assessed following treatment, increased with romiplostim dose from 0% at 1 μg/kg to 50% at 3 μg/kg and 100% at 6 μg/kg (Table 2). By day 11, one of four patients (25%) treated with romiplostim 1 μg/kg also had a platelet response. Overall, seven of the 12 patients (58.3%) achieved platelet responses, including six of eight patients (75.0%) treated with doses of 3 or 6 μg/kg. As shown in Table 2, romiplostim produced dose-related increases in the other efficacy measures. The mean peak platelet count ranged from $44 \times 10^9$/L at 1 μg/kg to $374 \times 10^9$/L at 6 μg/kg,

**Fig. 2** Patient disposition

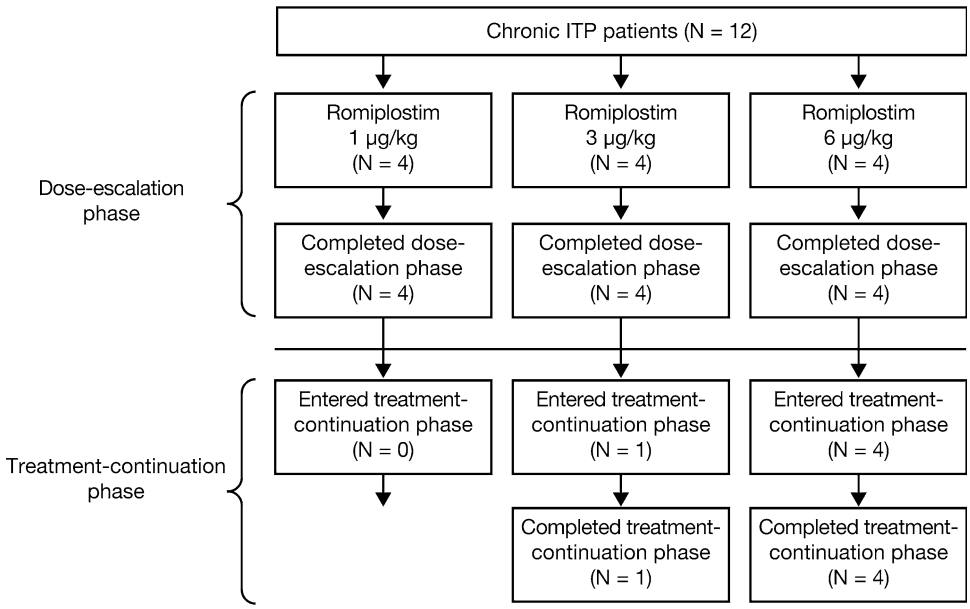


**Table 1** Patient demographics and baseline characteristics

| Characteristic | Dose cohort | | | |
|---|---|---|---|---|
| | 1 μg/kg ($n = 4$) | 3 μg/kg ($n = 4$) | 6 μg/kg ($n = 4$) | Total ($N = 12$) |
| Sex, *n* (%) | | | | |
| Female | 2 (50.0) | 3 (75.0) | 3 (75.0) | 8 (66.7) |
| Age (years), mean (SD) | 61.5 (1.3) | 52.0 (13.7) | 53.3 (7.2) | 55.6 (9.2) |
| Years since diagnosis, mean (SD) | 11.1 (7.1) | 9.0 (4.7) | 10.9 (5.9) | 10.3 (5.5) |
| Baseline platelet counts $\times 10^9$/L | | | | |
| Mean (SD) | 9.8 (5.8) | 8.8 (9.4) | 16.8 (13.0) | 11.8 (9.7) |
| Range | 4–15 | 3–23 | 5–31 | 3–31 |
| Corticosteroids, *n* (%) | | | | |
| Prior use | 3 (75.0) | 4 (100) | 4 (100) | 11 (91.7) |
| Concurrent use | 2 (50.0) | 3 (75.0) | 2 (50.0) | 7 (58.3) |
| Previous splenectomy, *n* (%) | 1 (25.0) | 0 (0) | 2 (50.0) | 3 (25.0) |
| Number of prior ITP therapies[a], mean (SD) | 4.5 (3.3) | 4.0 (2.1) | 3.5 (2.3) | 4.0 (2.6) |

[a] Excluding splenectomy

with the proportion of patients achieving various cut points for response, including platelet count $\geq 20 \times 10^9$/L above baseline and platelet count $\geq 50 \times 10^9$/L or $\times$ 100 $\times 10^9$/L, also increasing with romiplostim dose. All four patients in the 6-μg/kg cohort achieved these levels of peak response. When compared with the platelet count at baseline, the absolute change ranged from 34 $\times 10^9$/L at 1 μg/kg to 357 $\times 10^9$/L at 6 μg/kg, with the peak values representing a mean 4.1- to 26.2-fold increase above baseline. The mean time to peak response was approximately 13 days and did not differ by dose.

All 12 patients received both scheduled doses of romiplostim. The mean (SD) total dose of romiplostim was 116 ± 18 μg in the 1-μg/kg cohort, 360 ± 70 μg in the 3-μg/kg cohort, and 718 ± 116 μg/kg in the 6-μg/kg cohort. None of the patients received rescue medication.

Romiplostim was well tolerated. Overall, eight patients (66.7%) experienced at least one adverse event, most of which were mild in severity (Table 3). No severe, serious, or life-threatening adverse events were reported, and no patient withdrew due to an adverse event. Six patients (50.0%) had treatment-related adverse events, most commonly headache ($n = 3$; 25.0%). There was no apparent relationship between the romiplostim dose and the incidence of treatment-related adverse events. Other than changes in platelet counts, there were no clinically significant changes in other serum chemistry, hematology, or coagulation laboratory values during the course of the

dose-escalation phase. Similarly, no clinically significant changes in vital signs were observed.

Four patients had adverse events of bleeding. One patient in the 1-μg/kg cohort experienced epistaxis on day 21 (i.e., 13 days after the last dose of romiplostim). The platelet count was not recorded on the day of epistaxis, but was $9 \times 10^9$/L on the following day when the patient also experienced mouth hemorrhage. Another patient in the 1-μg/kg group had purpura and tongue hematoma on day 8, which was the day of the second romiplostim dose. This patient never achieved a response to romiplostim and had a platelet count of $2 \times 10^9$/L at the time of the bleeding event. One patient in the 3-μg/kg cohort experienced epistaxis on day 12. This subject had platelet counts of $199 \times 10^9$/L and $361 \times 10^9$/L when measured 2 days before and 3 days after the bleeding event, respectively. Finally, one patient in the 6-μg/kg cohort experienced purpura on day 31 (23 days after the second romiplostim dose); the platelet count was $17 \times 10^9$/L on the day of the bleeding event and $38 \times 10^9$/L when measured 5 days later.

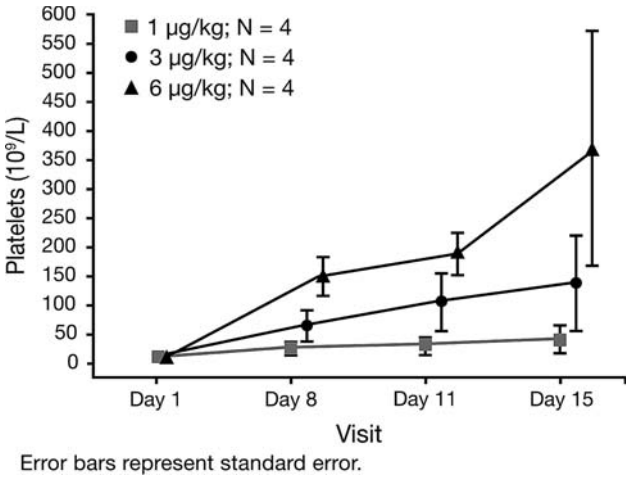


**Fig. 3** Mean platelet counts in the dose-escalation phase by romiplostim dose

All patients had a baseline sample and at least one post-baseline sample for testing for the presence of antibodies induced by romiplostim exposure. All tested samples were negative for binding antibodies to romiplostim, the active peptide portion of romiplostim, and TPO in the immunoassay, and therefore no samples were evaluated in the cell-based bioassay.

### 3.3 Treatment-continuation phase

Five patients entered the treatment-continuation phase, including one patient from the 3-μg/kg cohort and all four patients from the 6-μg/kg cohort. The patient who received romiplostim 3 μg/kg had a baseline platelet count of $6 \times 10^9$/L and values ranging from 19 to $115 \times 10^9$/L during the treatment-continuation phase. Approximately, half of these weekly assessments showed platelet counts of $>50 \times 10^9$/L (Fig. 4). Mean platelet counts in the four patients who received romiplostim 6 μg/kg generally remained $\geq 100 \times 10^9$/L through week 13, although values varied widely among the individual patients. By week 14, mean platelet counts had declined to $24 \times 10^9$/L, and no additional doses of romiplostim were given under the study

**Table 2** Platelet responses to romiplostim in the dose-escalation phase

| Efficacy measure | Dose cohort | | | |
|---|---|---|---|---|
| | 1 μg/kg ($n = 4$) | 3 μg/kg ($n = 4$) | 6 μg/kg ($n = 4$) | Total ($N = 12$) |
| Platelet response, *n* (%) | 1 (25.0) | 2 (50.0) | 4 (100) | 7 (58.3) |
| Day 8 | 0 (0) | 2 (50.0) | 4 (100) | 6 (50.0) |
| Day 11 | 1 (25.0) | 2 (50.0) | 4 (100) | 7 (58.3) |
| Day 15 | 1 (25.0) | 2 (50.0) | 4 (100) | 7 (58.3) |
| Platelet count $\geq 20 \times 10^9$/L over baseline, *n* (%) | 2 (50.0) | 3 (75.0) | 4 (100) | 9 (75.0) |
| Platelet count $\geq 50 \times 10^9$/L, *n* (%) | 1 (25.0) | 2 (50.0) | 4 (100) | 7 (58.3) |
| Platelet count $\geq 100 \times 10^9$/L, *n* (%) | 1 (25.0) | 2 (50.0) | 4 (100) | 7 (58.3) |
| Platelet count $\geq 450 \times 10^9$/L, *n* (%) | 0 (0) | 0 (0) | 1 (25.0) | 1 (8.3) |
| Peak platelet count $\times 10^9$/L | | | | |
| Mean (SE) | 44.0 (24.6) | 145.8 (80.8) | 374.3 (202.1) | 188.0 (78.1) |
| Range | 5–116 | 8–361 | 153–980 | 5–980 |
| Change from baseline in peak platelet count | | | | |
| Fold increase, mean (SE) | 4.1 (1.6) | 15.9 (6.3) | 26.2 (7.2) | 15.4 (4.0) |
| Absolute change $\times 10^9$/L, mean (SE) | 34.3 (23.0) | 137.0 (76.5) | 357.4 (199.4) | 176.2 (76.5) |
| Time to peak platelet count—days, mean (SE) | 13.3 (1.8) | 11.5 (1.4) | 14.0 (1.0) | 12.9 (0.8) |

**Table 3** Summary of safety during the dose-escalation phase

| Safety parameter, *n* (%) | Dose cohort | | | |
|---|---|---|---|---|
| | 1 μg/kg ($n = 4$) | 3 μg/kg ($n = 4$) | 6 μg/kg ($n = 4$) | Total ($N = 12$) |
| At least 1 adverse event | 3 (75.0) | 3 (75.0) | 2 (50.0) | 8 (66.7) |
| Serious or severe adverse event | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Treatment-related adverse event | 1 (25.0) | 3 (75.0) | 2 (50.0) | 6 (50.0) |
| Headache | 1 (25.0) | 1 (25.0) | 1 (25.0) | 3 (25.0) |
| Fatigue | 1 (25.0) | 0 (0) | 0 (0) | 1 (8.3) |
| Back pain | 0 (0) | 1 (25.0) | 0 (0) | 1 (8.3) |
| Muscle tightness | 0 (0) | 1 (25.0) | 0 (0) | 1 (8.3) |
| Flushing | 0 (0) | 0 (0) | 1 (25.0) | 1 (8.3) |
| Withdrawals due to adverse events | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Rescue medication use | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Anti-romiplostim neutralizing antibodies | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

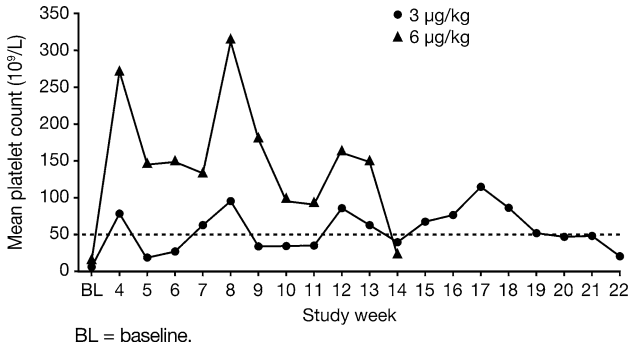


**Fig. 4** Mean platelet counts in the treatment-continuation phase by romiplostim dose

protocol due to the completion of the study. However, all five patients in the treatment-continuation phase subsequently entered an open-label extension study to continue romiplostim treatment.

The patients who participated in the treatment-continuation phase received a mean of $10 \pm 4.8$ doses of romiplostim. The patient in the 3-μg/kg cohort received 18 doses of romiplostim (all doses at 3 μg/kg; total dose 3240 μg). The four patients in the 6-μg/kg cohort received a mean of $8 \pm 2$ doses (one patient had all doses at 6 μg/kg; three patients had doses adjusted ranging from 0 to 5 μg/kg; mean total dose 2581 μg; range 1775–3030 μg). None of the subjects received rescue medication during the treatment-continuation phase.

The safety and tolerability of romiplostim was comparable to that observed during the dose-escalation phase. No severe, serious, or life-threatening adverse events were reported, and no patient withdrew due to an adverse event. Three patients (60%) had adverse events, most frequently contusion in two subjects receiving the 6-μg/kg dose. Two of the five patients had treatment-related adverse events, with malaise, arthralgia, and contact dermatitis each occurring in one patient treated with 6 μg/kg (Table 4). There were no adverse events of bleeding. Other than the changes in platelet counts, no clinically significant changes were noted in other serum chemistry, hematology, or coagulation laboratory values or clinically significant changes in vital signs during the treatment-escalation phase. Similarly, binding antibodies were not detected by immunoassay in any of the patients.

**Table 4** Summary of safety during the treatment-continuation phase

| Safety parameter, *n* (%) | 3 μg/kg ($n = 1$) | 6 μg/kg ($n = 4$) | Total ($N = 5$) |
|---|---|---|---|
| At least 1 adverse event | 0 (0) | 3 (75.0) | 3 (60.0) |
| Serious or severe adverse event | 0 (0) | 0 (0) | 0 (0) |
| Treatment-related adverse event | 0 (0) | 2 (50.0) | 2 (40.0) |
| Malaise | 0 (0) | 1 (25.0) | 1 (20.0) |
| Arthralgia | 0 (0) | 1 (25.0) | 1 (20.0) |
| Contact dermatitis | 0 (0) | 1 (25.0) | 1 (20.0) |
| Withdrawals due to adverse events | 0 (0) | 0 (0) | 0 (0) |
| Rescue medication use | 0 (0) | 0 (0) | 0 (0) |
| Anti-romiplostim neutralizing antibodies | 0 (0) | 0 (0) | 0 (0) |

## 4 Discussion

The results of this phase II study show that romiplostim treatment appears to be safe and well tolerated by Japanese patients with chronic ITP. Moreover, this study provides evidence that romiplostim is effective in stimulating platelet count increases in these Japanese patients. All four patients treated with a dose of 6 μg/kg and one half of

those treated with 3 μg/kg achieved platelet responses, which were defined as a doubling of the platelet count above the baseline to a level $\geq 50 \times 10^9$/L. Romiplostim produced dose-dependent effects on other measures of platelet production, including mean and maximum platelet counts, and the fold increase over baseline in platelet counts. None of the patients required rescue medication during the course of this study, and none had severe, serious, or life-threatening adverse events. Importantly, neutralizing antibodies to romiplostim or to endogenous TPO were not detected.

The dosing schedule used in this study was based on the results from the phase II study in Western populations, which evaluated whether a weekly dose of romiplostim (1, 3, or 6 μg/kg) would produce platelet counts within the target range of 50–450 $\times 10^9$/L [17]. This target platelet range was achieved by 10 of 16 patients who received romiplostim 1 or 3 μg/kg weekly for 6 weeks, although two patients had peak platelets counts above the target range. In the present study, romiplostim was administered weekly for 2 weeks producing platelet responses in one of four patients treated with 1 μg/kg, two of four patients treated with 3 μg/kg, and all four patients treated with 6 μg/kg. In the continuation phase of the present study, romiplostim was administered weekly at a dose of 3 μg/kg in one patient and 6 μg/kg in four patients, and generally maintained platelet counts within the desired range on most weeks. There were no bleeding events or rescue medications used in the continuation phase.

On the basis of the Western phase I/II studies, two parallel 24-week phase III trials of romiplostim were conducted in splenectomized and non-splenectomized patients [20]. Romiplostim was started at a dose of 1 μg/kg weekly, and then dose adjustment rules were used to achieve and maintain platelet counts within the range of 50–200 $\times 10^9$/L. Most patients, whether splenectomized or not, achieved overall platelet responses with romiplostim, with platelet counts $\geq 50 \times 10^9$/L for an average of 14–15 weeks of the 24-week treatment period. The primary study end point, durable platelet responses, which were defined by platelet counts $\geq 50 \times 10^9$/L for at least 6 of the last 8 weeks of treatment without need for rescue medication, were achieved significantly more often with romiplostim than with placebo in both splenectomized patients (38 vs. 0%; $P = 0.0013$) and non-splenectomized patients (61 vs 5%; $P < 0.001$). These findings illustrate the importance of individualizing the romiplostim dose in order to maintain platelet responses in patients with ITP. Dose adjustments were not made in the current study.

The most common treatment-related adverse event during dose escalation in this study was headache, which was reported by 3 of 12 patients (25%), whereas no treatment-related adverse event was reported by more than one patient during the treatment-continuation phase. Moreover, there were no discontinuations due to adverse events. These findings are consistent with the safety profile reported for romiplostim in the clinical studies conducted in Western ITP patient populations [17, 18, 20, 21].

The ability to draw conclusions from the present study is limited by the small number of patients treated. Phase III and extension studies are currently in progress to more fully evaluate the long-term safety and efficacy of romiplostim in Japanese patients with chronic ITP. The results from an open-label study of romiplostim in ITP patients from the United States and Europe have recently been published, with some patients treated for up to 3 years [23].

In summary, this phase II study shows that romiplostim is safe and well tolerated in Japanese patients and produces platelet responses over the dose range of 1–6 μg/kg, which is consistent with the results in Western populations. Based on these findings, a starting dose of 3 μg/kg was recommended for the phase III study of romiplostim in Japanese patients.

**Acknowledgments** This study was sponsored by Amgen KK (Japan). The authors would like to thank Yoshiaki Ogawa, Tokai University; and Kiyoshi Kitamura for providing for study support. M. Ohkura and Y. Sonehara, former employees of Amgen KK, provided biostatistical and study management support, respectively. Editorial support for the manuscript was provided by B. Weichman, PhD, and PAREXEL, and was funded by Amgen Inc.

**Conflict of interest statement** D. P. Berger is an employee of Amgen Inc. T. Ohtsu is a former employee of Amgen KK. Y. Shirasugi, K. Ando, S. Hashino, T. Nagasawa, Y. Kurata, Y., Kishimoto, and K. Iwato received research funding from Amgen.

## References

1. British Committee for Standards in Haematology General Hematology Task Force. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol. 2003;120:574–96. doi:10.1046/j.1365-2141.2003.04131.x.
2. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med. 2002;346:995–1008. doi:10.1056/NEJMra010501.
3. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996;88:3–40.
4. McMillan R. The pathogenesis of chronic immune thrombocytopenic purpura. Semin Hematol. 2007;44:S3–11. doi:10.1053/j.seminhematol.2007.11.002.
5. Bromberg ME. Immune thrombocytopenic purpura: the changing therapeutic landscape. N Engl J Med. 2006;355:1643–5. doi:10.1056/NEJMp068169.
6. Cines DB, McMillan R. Management of adult idiopathic thrombocytopenic purpura. Annu Rev Med. 2005;56:425–42. doi:10.1146/annurev.med.56.082103.104644.
7. George JN, Kojouri K, Perdue JJ, Vesely SK. Management of patients with chronic, refractory idiopathic thrombocytopenic

purpura. Semin Hematol. 2000;37:290–8. doi:10.1016/S0037-1963(00)90107-0.
8. Chang M, Nakagawa PA, Williams SA, Schwartz MR, Imfeld KL, Buzby JS, et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. Blood. 2003;102:887–95. doi:10.1182/blood-2002-05-1475.
9. McMillan R, Wang L, Tomer A, Nichol J, Pistillo J. Suppression of in vitro megakaryocyte production by antiplatelet autoantibodies from adult patients with chronic ITP. Blood. 2004;103:1364–9. doi:10.1182/blood-2003-08-2672.
10. Kosugi S, Kurata Y, Tomiyama Y, Tahara T, Kato T, Tadokoro S, et al. Circulating thrombopoietin level in chronic immune thrombocytopenic purpura. Br J Haematol. 1996;93:704–6. doi:10.1046/j.1365-2141.1996.d01-1702.x.
11. Mukai HY, Kojima H, Todokoro K, Tahara T, Kato T, Hasegawa Y, et al. Serum thrombopoietin (TPO) levels in patients with amegakaryocytic thrombocytopenia are much higher than those with immune thrombocytopenic purpura. Thromb Haemost. 1996;76:675–8.
12. Kuter DJ. New thrombopoietic growth factors. Blood. 2007;109:4607–16. doi:10.1182/blood-2006-10-019315.
13. Nomura S, Dan K, Hotta T, Fujimura K, Ikeda Y. Effects of pegylated recombinant human megakaryocyte growth and development factor in patients with idiopathic thrombocytopenic purpura. Blood. 2002;100:728–30. doi:10.1182/blood.V100.2.728.
14. Li J, Yang C, Xia Y, Bertino A, Glaspy J, Roberts M, et al. Thrombocytopenia caused by the development of antibodies to thrombopoietin. Blood. 2001;98:3241–8. doi:10.1182/blood.V98.12.3241.
15. Broudy VC, Lin NL. AMG531 stimulates megakaryopoiesis in vitro by binding to Mpl. Cytokine. 2004;25:52–60. doi:10.1016/j.cyto.2003.05.001.
16. Nichol JL. AMG 531: an investigational thrombopoiesis-stimulating peptibody. Pediatr Blood Cancer. 2006;47:723–5. doi:10.1002/pbc.20972.
17. Bussel JB, Kuter DJ, George JN, McMillan R, Aledort LM, Conklin GT, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. N Engl J Med. 2006;355:1672–81. doi:10.1056/NEJMoa054626.
18. Newland A, Caulier MT, Kappers-Klunne M, Schipperus MR, Lefrere F, Zwaginga JJ, et al. An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura. Br J Haematol. 2006;135:547–53. doi:10.1111/j.1365-2141.2006.06339.x.
19. Wang B, Nichol JL, Sullivan JT. Pharmacodynamics and pharmacokinetics of AMG 531, a novel thrombopoietin receptor ligand. Clin Pharmacol Ther. 2004;76:628–38. doi:10.1016/j.clpt.2004.08.010.
20. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008;371:395–403. doi:10.1016/S0140-6736(08)60203-2.
21. Kumagai Y, Fujita T, Ozaki M, Sahashi K, Ohkura M, Ohtsu T, et al. Pharmacodynamics and pharmacokinetics of AMG 531, a thrombopoiesis-stimulating peptibody, in healthy japanese subjects: a randomized, placebo-controlled study. J Clin Pharmacol. 2007;47:1489–97. doi:10.1177/0091270007306563.
22. Nakagawa M. Idiopathic thrombocytopenic purpura: a practice guideline for diagnosis and treatment of intractable diseases. ed Rev. ed. Tokyo: Roppo shuppansha; 2001.
23. Bussel JB, Kuter DJ, Pullarkat V, Lyons RM, Guo M, Nichol JL. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic itp. Blood. 2009;113:2161–71. doi:10.1182/blood-2008-04-150078.