Self-administration of romiplostim in patients with chronic immune thrombocytopenia

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Background Romiplostim increases platelet counts in ITP and is typically injected at clinic visits.

Objective To estimate the efficacy and safety of romiplostim self-administration, we evaluated data from an open-label extension study in a post hoc analysis.

Methods Patients received weekly romiplostim with dose adjustments to target platelet counts of 50-200 $\times$ 10^9/L. Patients with a stable dose and platelet counts of 50-200 $\times$ 10^9/L $\geq$ 3 weeks could begin self-administration if investigators deemed it appropriate, returning to study sites every 4 weeks.

Results Of 292 patients, 239 (82%) initiated self-administration for a median of 74 (Q1-Q3:56-164) weeks. Twenty-eight of the 239 (12%) discontinued self-administration (investigator or sponsor decision: 19, patient request: 6, noncompliance: 3). The median average weekly dose for patients self-administering romiplostim was 4.1 μg/kg. The romiplostim dose was adjusted in 40 (17%) of the 239 patients in the first 8 weeks of self-administration; 84 (35%) in the first 6 months. Patients had a platelet response ($>$ 50 $\times$ 10^9/L) for a mean of 75.1% of weeks. The adverse event (AE) rate was 18.3/100 patient-weeks, with 0.8 serious AEs/100 patient-weeks. Fourteen AEs led to withdrawal; none related to self-administration.

Limitations The analysis was post hoc. Lack of a randomized comparator group may have resulted in differences between patient populations. No distinctions could be made between constant and intermittent self-administration or between adverse events occurring during self-administration or administration at the study site.

Conclusions Patients were able to maintain platelet responses for a mean of 75% of the time without new safety issues while self-administering romiplostim.

Chronic immune thrombocytopenia (ITP) is an autoimmune disorder characterized by decreased platelet production and immune-mediated platelet destruction.[1] Romiplostim is an Fc-peptide fusion protein (peptibody) shown to increase platelet counts in thrombocytopenic patients with ITP[2-11] and is associated with improved health-related quality-of-life in responders.[12,13]

Currently, in the United States, romiplostim is approved for weekly subcutaneous administration by

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TABLE 1 Patients who completed a previous romiplostim study, entered the extension study, and were included in the analysis of self-administration (N = 292)

No. and design of previous study	Completed previous study, n	Allowed self-administration in previous study, n	Adult patients who continued in extension study, n
1[a] Open-label, dose escalation trial[4]	23	0	16
2[a] Double-blind, placebo-controlled trial[4]	17	0	14
3 Open-label, dose-escalation trial[5]	16	0	8
4[b] Double-blind, placebo-controlled in splenectomized patients[2]	59	0	52
5[b] Double-blind, placebo-controlled in nonsplenectomized patients[2]	56	0	50
6 Open-label, romiplostim vs. medical standard-of-care treatment[3]	202	96[c]	136
7 Single-arm study[9]	288	2[c]	16
Total patients	661	98	292

[a] The results of studies 1 and 2 were reported in a single publication; [b] The results of studies 4 and 5 were reported in a single publication; [c] If the investigator felt that self-administration was appropriate for a patient who had a stable dose of romiplostim and platelet counts in the target range for ≥ 3 weeks, the patient could choose to receive training and then self-administer romiplostim.

a health care provider. In some romiplostim clinical studies, administration of romiplostim outside of the health care setting by the patient or a trained caregiver (ie, self-administration) was an option and was evaluated. Self-administration requires several steps, including appropriate handling of romiplostim vials before use (protection from light and refrigerated storage at 36°F to 46°F [2°C to 8°C]), aseptic reconstitution of the powder into a solution, and proper administration of the correct dose. This last step is of special concern as reconstitution of the prescribed dose may result in a small volume (eg, 0.3 mL) to be injected. However, for those patients able to consistently carry out these steps, romiplostim self-administration offers improved convenience and a sense of greater control of their disease.

Self-administration of romiplostim has been evaluated in a long-term, single-arm, open-label extension study in which all patients received romiplostim. The adult patient population of the extension study comprised 292 patients who had completed one of seven previous studies of romiplostim (Table 1[2-5,9] [note that two publications[2,4] described two studies each]). In these previously completed studies, patients could have received romiplostim or placebo, as well as rescue medication, or medical standard-of-care treatment. In one of the previously completed single-arm studies[9] and in the romiplostim versus medical standard-of-care study,[3] if the investigator felt that self-administration was appropriate for a patient who had a stable dose of romiplostim and platelet counts in the target range for ≥ 3 weeks, the patient could choose to receive training and then self-administer romiplostim. In the other studies, all patients received romiplostim at the study site.

We conducted a post hoc analysis to estimate the efficacy and safety of romiplostim self-administration in ITP in the 292 patients from the long-term open-label extension study to assess outcomes in patients electing self-administration and to see if these outcomes were similar to those in patients who received all of their romiplostim injections at clinical trial study sites.

Methods

Study design

Patients who had completed one of seven prior romiplostim studies (Table 1),[2-5,9] regardless of whether they had been randomized to romiplostim, placebo, or medical standard-of-care treatment, were eligible to enter this open-label extension study. Data collected from these patients during the extension study were the basis for this evaluation of self-administration. Over the course of the extension study, the protocol was amended several times to change the maximum allowed dose (10-30 μg/kg) and/or the platelet count ($\leq 50 \times 10^9$/L or no restriction) required to enter the extension, in part on the basis of the previously completed studies. The target platelet count range also changed from 50-250 $\times 10^9$/L to 50-200 $\times 10^9$/L. The patients in the extension study were followed at 109 sites in the United States, Canada, Europe, and Australia. The feasibility and durability of voluntary self-administration was evaluated until completion of the extension study; thus, the evaluation includes information drawn from 292 patients receiving romiplostim from 1 to 277 weeks (5.3 years). Previously, data were published from 90 patients receiving romiplostim for up to 3 years;[10]

this manuscript describes data from an additional 202 patients (292 total) over a longer period of time. Results regarding the final analysis of all 292 patients have been published.[11] The extension study protocol was approved by the institutional review board at each study site before any patients were enrolled at that site (ClinicalTrials.gov Identifier NCT00116688). This study was funded by Amgen Inc, which designed the study, collected and helped analyze the data, and provided medical writing support. Publication decisions were made by the authors in conjunction with Amgen.

Patients and treatment

All patients or their legally acceptable representatives gave written informed consent before any screening procedures were performed. The previously completed studies enrolled thrombocytopenic patients with ITP as defined by the American Society of Hematology.[14] Although both children and adults were enrolled in the extension study, only adults (18 years or older) are included in these analyses. As there are additional considerations for romiplostim self-administration in children, results from pediatric patients will be reported separately. Continuation of romiplostim treatment after the prior study was at the discretion of the investigator.

All patients received weekly subcutaneous injections of romiplostim as described previously.[10,11] Romiplostim doses were adjusted to achieve a target platelet count of 50-200 $\times$ 10^9/L. If the investigator felt that self-administration was appropriate for a patient who had a stable dose of romiplostim and platelet counts in the target range for $\geq$ 3 weeks, the patient could choose to receive training and then self-administer romiplostim. Patients who were self-administering romiplostim during a previously completed study[3,9] were permitted to continue self-administration after entering the extension study. All patients who self-administered romiplostim returned to the study site every 4 weeks for evaluation and supplies. If any dose changes were made during a study site visit, patients returned to the clinic during each of the following 2 weeks so that the investigator could confirm that the dose change resulted in appropriate platelet counts. Patients who did not self-administer romiplostim returned to the study site weekly to receive their injections.

The investigator was responsible for ensuring that patients or caregivers were adequately trained and capable of administering treatment. Patients or caregivers received training on preparing and administering the injection from staff at the study site and from a specially prepared DVD and descriptive mat. Once patients/caregivers had demonstrated their ability to reliably administer romiplostim, they were given 3.0-mL disposable syringes (to reconstitute romiplostim), 1.0-mL disposable syringes (to administer romiplostim), 18- and 27-gauge needles, and 500-μg vials of romiplostim. Patients used one or two vials of romiplostim as necessary for their particular dose. During study visits, site personnel were to ensure that each patient was supplied with all necessary materials required for self-injection, and patients were required to return all used and unused vials of romiplostim for assessment of compliance and drug accountability.

All patients received diaries in which to record the date, time, and volume of drug administered; these diaries were to be returned to study staff. Study site personnel recorded whether or not the patient began self-administration during the extension study, whether or not the patient continued self-administration until the end of the extension study, and the dates the patient initiated and permanently discontinued self-administration. The location at which each individual dose was administered, whether patients temporarily discontinued self-administration, and whether doses were administered by the patient or a caregiver were not recorded. Visiting nurses were not part of the study. Compliance with dosing was assessed on the basis of diary entries and returned vials of romiplostim.

Assessments

The screening visit for the extension study occurred within 30 days before the week 1 visit, and included a physical examination and a complete blood count. Throughout the extension study, at every study site visit, platelet counts were performed, concomitant medications were documented, and adverse events were assessed. Whether these events occurred when romiplostim was being self-administered or administered at the study site was not reported.

Statistical analysis

All analyses were post hoc. Summary statistics were calculated to assess the long-term exposure to romiplostim, maintenance of self-administration, and the long-term efficacy and safety of self-administration. Maintenance of self-administration was evaluated on the basis of the percentage of patients who maintained self-administration. Long-term efficacy was evaluated on the basis of platelet counts over time and the percentage of weeks during which patients achieved a platelet response. Platelet response was defined as a platelet count of $>$ 50 $\times$ 10^9/L without use of rescue medication in the previous 8 weeks. Safety was assessed on the basis of the incidence of adverse events, including clinically significant changes in laboratory values (especially those changes requiring therapy or adjustment of existing therapies). Efficacy and safety data collected during the 3 weeks before patients initiated romiplos-

TABLE 2 Patient demographics and baseline characteristics

Characteristic	Electing self-administration		Total[a] (N = 292)
	Yes (n = 239)	No (n = 52)	
Age (median, Q1, Q3), y	53.0 (43.0, 67.0)	56.0 (39.5, 69.5)	54.0 (43.0, 68.0)
Sex, female, n (%)	152 (63.6)	32 (61.5)	184 (63.2)
Race, n (%)			
Caucasian	205 (85.8)	40 (76.9)	245 (84.2)
African American	7 (2.9)	6 (11.5)	13 (4.5)
Hispanic	16 (6.7)	5 (9.6)	21 (7.2)
Other[b]	11 (4.6)	1 (2)	12 (4.1)
Baseline platelet count, (median, Q1, Q3), $\times 10^9$/L	39.0 (17.0, 109.0)	20.5 (12.5, 46.0)	35.0 (15.0, 100.0)
Previous splenectomy, n (%)	74 (31.0)	21 (40.4)	95 (32.5)

Q1, Q3 = 25th [Q1] and 75th [Q3] percentiles.
[a] One patient who was enrolled in the extension study discontinued before receiving romiplostim; [b] Other includes Asian, American Indian or Alaska native, and Native Hawaiian or other Islander.

tim self-administration served as a baseline for self-administration, with patients serving as their own controls. While the actual romiplostim dose before and after the initiation of self-administration was examined, dosing adjustments were not compared due to bias from study design, as all patients who initiated romiplostim self-administration were required to have a stable romiplostim dose for 3 weeks prior to initiation of self-administration.

Results

Patient disposition

A total of 292 patients enrolled in this open-label extension study; one patient withdrew from the study before receiving romiplostim. In previous studies, all patients had been receiving investigational product (romiplostim or placebo) at the study site throughout, except for 96 of the 136 patients from the romiplostim and medical standard-of-care study and 2 patients from one of the open-label single-arm studies (Table 1). These 98 patients had already been self-administering romiplostim during their previous study.[3,9] During this extension study, 141 (73%) of the 194 patients who had not previously been self-administering romiplostim chose to initiate romiplostim self-administration. Therefore, a total of 239 (82%) of the 292 patients in this extension study self-administered romiplostim. At entry to the extension study, the demographic characteristics of patients who chose (239 patients) and did not choose (52 patients) to initiate self-administration were similar with respect to sex and median age, but not median baseline platelet count (39.0×10^9/L vs. 20.5×10^9/L; Table 2). Slightly lower percentages of African American and Hispanic patients were among those who initiated self-administration of romiplostim.

Long-term exposure to romiplostim and maintenance of self-administration

The median average weekly romiplostim dose in patients self-administering romiplostim was consistent over time (Figure 1). The overall median (25th percentile [Q1], 75th percentile [Q3]) average weekly dose was 4.1 μg/kg (2.1, 7.7 μg/kg), and the median (Q1, Q3) most frequently administered dose was 4.0 μg/kg (2.0, 8.0 μg/kg). Romiplostim dosing during self-administration was not different from dosing during the 3 weeks before self-administration (median average weekly dose: 4.0 μg/kg, median most frequently administered dose: 4.0 μg/kg).

The median duration of time from initiation to completion or termination of self-administration was 74 weeks (Q1, Q3: 56, 164 weeks; range: 3-244 weeks). Of the 239 patients who initiated self-administration, 28 (12%) discontinued self-administration: 19 because of investigator or sponsor decisions, 6 as a result of patient requests, and 3 due to noncompliance. The self-administration status of one patient at the end of the extension study was unknown. Thus, 88% (210/239) of patients who chose to initiate romiplostim self-administration, and 72% (210/292) of all patients in the study, were self-administering romiplostim at the end of the extension study.

Dose adjustments, which were made at study site visits, occurred at a duration-adjusted rate of 7.85/100 patient-weeks (1,892 adjustments in total) over the period of self-administration. The most common reasons for dose adjustments, which could include not receiving a dose, were per-protocol specifications (ie, adjusting for platelet counts) (66%), other (21%), noncompliance (9.2%), dose administration error (2.8%), and adverse event (1.2%). The duration-adjusted rate for adjustments other than those specified

in the protocol was 2.70/100 patient-weeks. The "other" category consisted of a variety of reasons, including doses missed because patients forgot or ran out of medication. Dose adjustments were categorized as non-compliance if a patient consistently missed doses and clinic visits. Dose administration errors, as reported by the study sites, included patients' incorrectly diluting romiplostim, using previous dose adjustment rules (as the rules changed during the course of the extension study), and administering the wrong volume (such as 0.4 mL instead of 0.32 mL). During the first 8 weeks after initiating self-administration, 199 patients (83%) had no dose adjustments, while 40 (17%) had one or two dose adjustments. Over the first 6 months of self-administration, 155 (65%) patients had no dose adjustments, while 76 (32%) had 1 or 2 dose adjustments, and 8 (3%) had 3 or more dose adjustments.

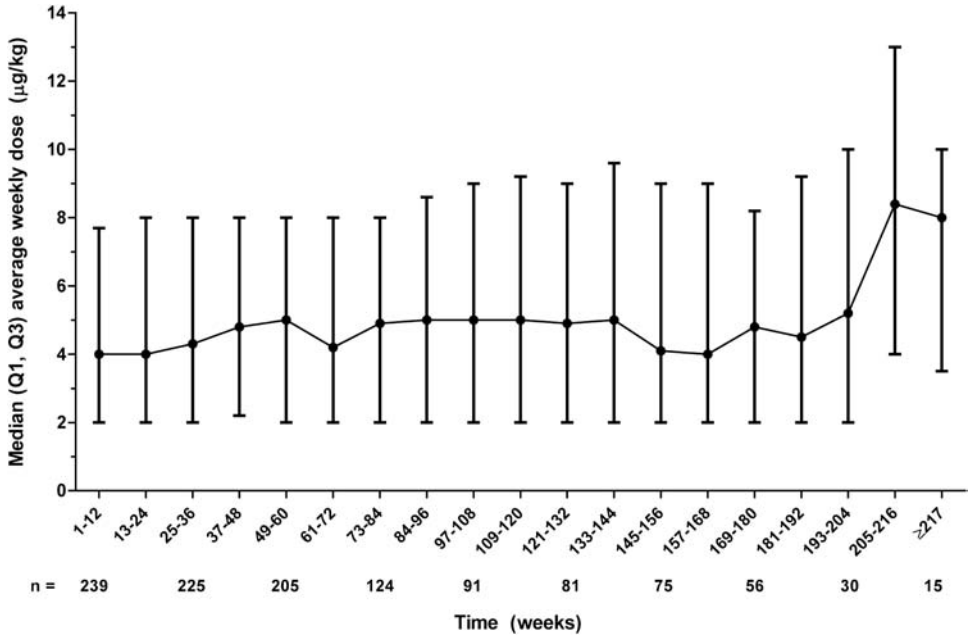

FIGURE 1 Median (25th [Q1], 75th [Q3] percentiles) average weekly dose in patients electing to self-administer romiplostim.

Efficacy

Median platelet counts for patients choosing self-administration remained steady throughout the extension study (Figure 2); large interquartile ranges were observed at some time points when the patients remaining in the study for very long periods became few and hence the sample size was small. During self-administration, platelet counts were $< 50 \times 10^9$/L for a mean 18.6% (SD, 26.2%) of the time, 50-200 $\times 10^9$/L for 54.7% (28.6%) of the time, 200-400 $\times 10^9$/L for 22.5% (24.1%) of the time, and $> 400 \times 10^9$/L for 4.2% (8.6%) of the time (Figure 3). This is similar to the distribution seen in the 3 weeks before initiation of self-administration (mean time in each platelet category was 14.1% for $< 50 \times 10^9$/L, 63.1% for 50-200 $\times 10^9$/L, 22.2% for $>$ 200-400 $\times 10^9$/L, and 0.6% for $> 400 \times 10^9$/L). The mean percentage of weeks patients had a platelet response (defined as platelet count of $> 50 \times 10^9$/L without use of rescue medication in the previous 8 weeks) was 82.4% in the 3 weeks prior to initiation of self-administration and 75.1% thereafter.

Safety

The adverse events most commonly reported by patients self-administering romiplostim were headache, contusion, epistaxis, and fatigue (Table 3). For patients self-administering romiplostim at any point during the extension study, the duration-adjusted adverse event rates over the course of the extension study were 18.3/100 patient-weeks for all adverse events and 0.8/100 patient-weeks for serious adverse events. Rates of these events remained steady or decreased over time.

Treatment-related adverse events (ie, romiplostim-related events) were reported at a rate of 0.9/100 patient-weeks, while treatment-related serious adverse events were reported at a rate of 0.1/100 patient weeks. No specific information was collected on causality of adverse events other than investigator attribution to romiplostim. Fourteen adverse events led to study withdrawal (rate of 0.06/100 patient-weeks). Of these, six were considered related to romiplostim (increased bone marrow reticulin, myocardial infarction, decreased platelet count, septic thrombophlebitis, multiple myeloma, and unstable angina), and eight were not (hepatic neoplasm malignant, myocardial infarction, pneumococcal sepsis, lymphoma, renal failure, cardiac tamponade, systemic lupus erythematosus rash, and death). The duration-adjusted rates (per 100 patient-weeks) at which patients reported adverse events and treatment-related adverse events were similar during the 3 weeks before initiation of self-administration and the remainder of the extension study (Table 4). The rates of serious adverse events were 0.3/100 patient-weeks before self-administration and 0.8/100 patient-weeks during self-administration; of note, only two events were observed in the 3 weeks before initiation of self-

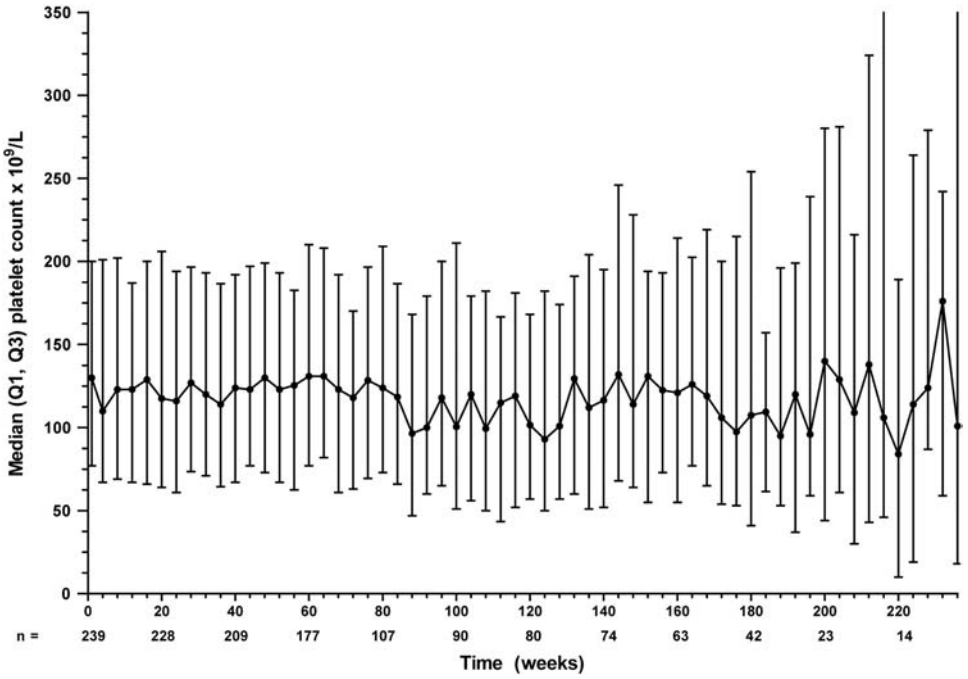

FIGURE 2 Median (Q1, Q3) weekly platelet counts of elective self-administration.

administration. There were no treatment-related serious adverse events in the 3 weeks before initiation of self-administration and 24 treatment-related serious adverse events in the period after initiation of self-administration (duration-adjusted rate of 0.1/100 patient-weeks).

Discussion and conclusion

In this open-label extension study of romiplostim in ITP, of those patients electing to begin or continue romiplostim self-administration (82% of all patients on study), most were able to achieve and maintain median platelet counts consistently between 100 and 150 $\times$ 10^9/L with a stable dose of romiplostim. The safety profile was not different than that seen in previous romiplostim studies.[2-9] On the basis of information from patients' diaries, the dose administration error rate was determined to be 2.8%. The increase in romiplostim dose after Week 200 likely reflects the change in patient characteristics as patients entered the extension study from different previous studies; some patients required higher doses throughout.[10,11] These results suggest that romiplostim self-administration for ITP patients is a feasible alternative to health-care–provider administration as long as adequate training can be provided and assessed.

Our findings are consistent with those from the much earlier report of this study and from an earlier, retrospective observational study of 80 patients participating in a romiplostim compassionate use program for ITP patients.[10,15] In the observational study, data from patients with severe chronic ITP who had been followed for 2 or more years after starting romiplostim were collected and analyzed. The first romiplostim injection was administered at a hospital, but thereafter administration by the patient or a visiting nurse was allowed; there were no specific rules dictating whether romiplostim was to be administered at the hospital or elsewhere or by the patient or by a nurse. Platelet counts were measured weekly until the dose was stabilized and monthly thereafter. Platelet response (platelet count $\geq$ 50 $\times$ 10^9/L and double the baseline count) was achieved in 74% of patients. This response rate, as well as the severity and frequency of adverse events, was similar to that in the pivotal romiplostim studies.[2] The report does not provide information on the percentages of patients who self-administered romiplostim nor does it compare responses between patients who did and did not elect to self-administer romiplostim. Nevertheless, this study provides additional evidence that self-administration of romiplostim is a feasible alternative to administration at the clinic or hospital. Although specific queries were not included to determine the benefits to the patients of self-administration, it would seem from the high percentages of patients initiating and sustaining self-care that there was a patient preference for the self-administration option.

The median, Q1, and Q3 of platelet counts at baseline (defined as the last non-missing platelet count on or before the initiation of self-administration) suggest that most patients had platelet counts in the target range at the time they started self-administration. This is likely because patients were required to maintain platelet counts above 50 $\times$ 10^9/L before they could start self-administration. Large interquartile ranges were observed at some time points when patients had remained in the study for long periods and the sample size was relatively small.

The median platelet count at baseline of the extension study for the 292 patients was 39.0 $\times$ 10^9/L. This count was low because the study entry criteria for many of the study patients required patients to have platelet counts $\leq$ 50 $\times$ 10^9/L before entering the study. After starting romiplostim treatment, these patients were able to maintain a platelet count in the target

range and therefore start self-administration. Figure 2 shows that the median, Q1, and Q3 for platelet counts at the time patients started self-administration (week 0) were in the target range.

There are several possible confounding factors for this extension study, including that assignment to self-administration was based on investigator and patient choice; thus, there was no randomized comparator group of patients. Patients with major efficacy or safety issues would be unlikely to be able to maintain platelet counts and a stable romiplostim dose, which could lead to differences in the populations of patients who did and did not begin self-administration. In addition, patients with higher platelet counts may have had less severe disease and thus may have been more likely to respond to romiplostim. It is also possible that patients who might otherwise have chosen self-administration may not have been considered suitable by the investigator for reasons unrelated to the patient's condition or response to romiplostim, such as compliance or perceived safety concerns.

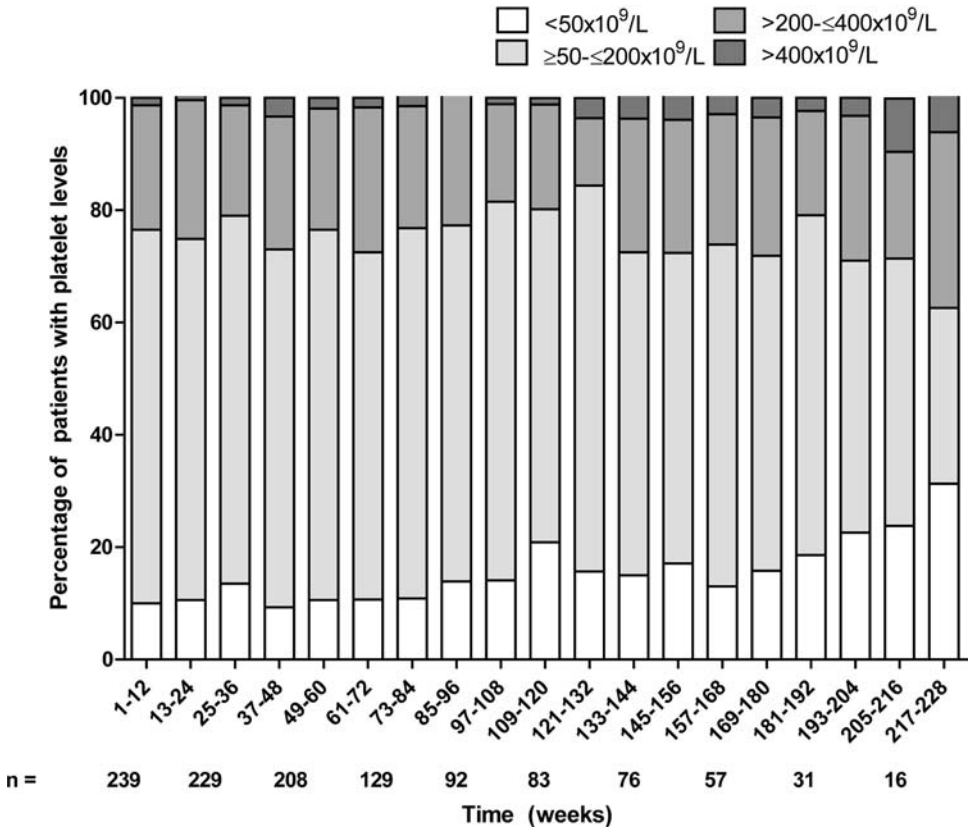

FIGURE 3 Proportions of patients electing self-administration with platelet counts < 50 × 10^9/L; ≥ 50 - ≤ 200 x 10^9/L; > 200 - ≤ 400 × 10^9/L; or > 400 ×10^9/L.

The design of the previous studies in which patients were enrolled could also affect results. For example, patients from the medical standard-of-care comparator study[3] and a single-arm study[9] had the option to self-administer romiplostim during those studies and hence would have been likely to continue to do so in this extension study if this approach had previously been effective for them. Patients from the medical standard-of-care comparator study[3] also had earlier stage disease (prior to splenectomy per study design) and no requirement for low platelet counts to enter the extension study. Patients enrolled in the extension study under previous protocol versions (ie, from other previous studies) were required to have an entry platelet count no greater than 50×10^9/L, so as to demonstrate a continued need for romiplostim after discontinuation from the previous study, which often happened only when romiplostim was discontinued.

The nature of the information available for post-hoc analyses also limits interpretation. For example, the data collected do not distinguish between constant and intermittent self-administration. Specifically, where and by whom each romiplostim dose was administered and whether patients temporarily discontinued self-administration was not recorded. Consequently, adverse event reporting was based on whether patients had self-administered romiplostim at any point during the study, not whether these adverse events occurred while patients were self-administering romiplostim or receiving romiplostim at the study site.

A study of the effects of ITP on healthcare-provider visits and workplace productivity showed that patients with ITP had more physician visits and worse scores on work and productivity measures than healthy age- and sex-matched controls.[16] Enabling patients to self-administer romiplostim would reduce the number of clinic visits and missed time from work or school. In addition, self-administration, by offering a more convenient treatment option, could be important for maintaining compliance.

In conclusion, in this extension study, most patients were able to achieve romiplostim self-administration, generally maintaining stable platelet counts without the need for dose adjustments. There were few issues with dosing errors, and the safety profile was similar to that

TABLE 3 Summary of study-duration–adjusted adverse event rates (per 100 patient-weeks) for patients electing self-administration (n = 239) during the entire extension study period[a]

Adverse event	Rate
Most commonly reported	
Headache	1.206
Contusion	0.992
Epistaxis	0.709
Fatigue	0.698
Nasopharyngitis	0.591
Arthralgia	0.467
Of interest	
Reticulin[b]	0.007
Hematologic malignancy	0.010
Thrombotic/thrombo-embolic events	0.066

[a] Period included time when patients were not self-administering romiplostim; [b] Bone marrow biopsies were not required but were performed at the discretion of the investigator. For the entire extension study population (N = 292), bone marrow biopsies were performed on 38 patients, usually because of a lack of response to treatment. Eleven of these patients had findings of reticulin, which were reported as adverse events by the investigator in 4 cases.

TABLE 4 Safety overview for patients initiating self-administration (N = 239)

	3 weeks before SA initiation: 657 patient-weeks, no. events (rate[a])	SA initiation to end of treatment: 24,642 patient-weeks, no. events (rate[a])
Adverse events	133 (20.3)	4,506 (18.3)
Treatment-related	12 (1.8)	221 (0.9)
Serious AE	2 (0.3)	209 (0.8)
Treatment-related	0 (0)	24 (0.1)

Abbreviations: AE, adverse event; n, number of events; SA, self-administration. [a] Rate is per 100 patient-weeks.

associated with administration of romiplostim at the study site. Thus, the analyses described here show that once a patient started self-administration, the efficacy and safety profiles were comparable with those seen in previous romiplostim studies in which all dosing was performed weekly at clinical study sites. Romiplostim self-administration could be part of a strategy in which individual patients could either self-administer romiplostim or receive romiplostim at the clinic according to the extent of variation in their platelet counts and romiplostim doses. Self-administration of romiplostim can thus provide greater convenience and independence for patients who require continued treatment for their ITP.

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