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ORIGINAL ARTICLE

Oral eltrombopag for up to three years is safe and well-tolerated in Japanese patients with previously treated chronic immune thrombocytopenia: an open-label, extension study

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Abstract Eltrombopag is an oral, nonpeptide, thrombopoietin receptor agonist approved for treatment of chronic immune thrombocytopenia (ITP). The safety, tolerability, and efficacy of eltrombopag for up to 3 years were evaluated in 19 Japanese patients with chronic ITP who had completed a prior 6-month study. Patients received eltrombopag once daily at the last dosage received in the prior study (12.5, 25, or 50 mg). Dose adjustments and treatment interruptions were permitted to maintain platelet counts of 50,000–200,000/μL. Primary evaluations were safety and tolerability of long-term eltrombopag treatment. The median duration of exposure was 27.5 months (range, 9.9–32.3). Adverse events were similar to those reported with short-term use of eltrombopag, and none led to treatment discontinuation. Nine serious adverse events were reported. Median platelet counts began to increase after 1 week of treatment and remained above 50,000/μL for most assessments. Bleeding episodes decreased from 63 % at baseline to 21 % after 2 weeks of treatment and remained below baseline for all assessments. Of 15 patients receiving concomitant baseline ITP medications, 10 permanently discontinued or achieved a sustained reduction of at least one treatment without requiring rescue treatment. Long-term treatment with eltrombopag was safe, well tolerated, and effective in Japanese patients with chronic ITP.

Keywords Bleeding · Platelets · Thrombopoietin receptor agonist

Introduction

Chronic immune thrombocytopenia (ITP) is characterized by isolated thrombocytopenia (platelet count <100,000/μL) in the absence of other causes of thrombocytopenia [1, 2]. In addition to autoimmune-mediated platelet destruction, reduced platelet production is an important cause of thrombocytopenia in patients with chronic ITP [2]. The incidence rate of newly diagnosed ITP in Japan between 2004 and 2007 was estimated at 2.16/100,000/year [3].

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The symptoms of ITP range from mild bruising to hemorrhage, but the major concern is risk of intracranial hemorrhage [4, 5]. The goal of treatment is to provide adequate platelet levels to prevent major bleeding while minimizing treatment-related toxicity. Generally, patients with a platelet count ≥50,000/μL can maintain hemostasis and require no treatment unless they have a history of bleeding or are at increased risk of bleeding [2]. Current first- and second-line approaches include corticosteroids and splenectomy; approximately 30 % of patients with chronic ITP remain refractory to these therapies [6–8]. For patients who are refractory or intolerant to these therapies, immunosuppressive agents or rituximab are common as third-line therapies, although these are not approved for treatment of chronic ITP in Japan [9].

Another therapeutic approach is to activate the receptor for thrombopoietin, the growth factor that regulates platelet production. Thrombopoietin receptor (TPO-R) agonists are an effective treatment for patients with refractory chronic ITP and are recommended as third-line therapy in a recent reference guide for management of chronic ITP in Japan [9]. Eltrombopag is an oral, nonpeptide, TPO-R agonist approved in multiple countries for the treatment of chronic ITP. Eltrombopag increases platelet production by interacting with the transmembrane domain of the TPO-R and inducing proliferation and differentiation of bone marrow progenitor cells in the megakaryocyte lineage [10, 11].

The approved starting daily dose of eltrombopag for treatment of chronic ITP in the United States and Europe is 50 mg; this is adjusted to 25 mg daily for patients of East Asian ancestry [11, 12]. The lower starting dose for East Asian patients is based on inter-ethnic differences in the pharmacokinetics of eltrombopag in healthy volunteers and patients with chronic ITP. A study in healthy Japanese males demonstrated area under the curve (AUC) values nearly twofold higher than those reported at similar doses in volunteers of European ancestry [13]; in an analysis of 5 clinical trials of both healthy volunteers and patients with chronic ITP, apparent clearance (CL/F) of eltrombopag was 33 % lower in patients of East Asian descent compared with other races [14].

The recent results of a Japanese study, consisting of a 6-week, randomized, double-blind, placebo-controlled phase and a 6-month, open-label phase, demonstrated that eltrombopag increased platelet counts and reduced the incidence of bleeding symptoms in Japanese patients with previously treated chronic ITP [15]. Based on these data, eltrombopag has been approved in Japan, and a dose of 12.5 mg once daily is recommended as the starting dose. However, this study was conducted within a relatively short follow-up period. In order to expand on these results, we conducted an extension study to assess the long-term safety, tolerability, and efficacy of eltrombopag in Japanese patients with chronic ITP who had completed the preceding 6-month study.

Materials and methods

Study population

Patients who had completed the protocol-defined treatment for 6 months in the previous Japanese eltrombopag ITP study, including the 4-week follow-up period, were enrolled. Eligibility criteria were based on the previous study; however, patients with baseline platelet count ≥50,000/μL at entry into this extension study or with an unstable dose of concomitant treatment for chronic ITP for 4 weeks before enrollment were also included. Patients were excluded if there were any significant changes in their medical conditions throughout the previous study.

Study design

This was an open-label, extension study designed to assess the long-term safety, tolerability, and efficacy of eltrombopag in Japanese patients with chronic ITP who had completed 6 months of eltrombopag treatment in a previous study [15]. This study protocol was approved by the institutional review board of participating centers and was conducted in accordance with the Declaration of Helsinki (as revised in Tokyo 2004), Good Clinical Practice guidelines, and local laws and regulations. All patients provided written informed consent.

Treatment continued until commercial availability of eltrombopag in Japan or occurrence of unacceptable adverse events (AEs). Patients who discontinued eltrombopag treatment were followed for 26 weeks to monitor safety. This study is registered at ClinicalTrials.gov (NCT00828750).

Treatment and dose adjustment

Eltrombopag was administered orally once daily in the fasting state. The starting dose for each patient was the last dose received in the previous 6-month study (12.5, 25, or 50 mg daily). Dose modification guidelines were similar to those used in the previous study [15]. Dose adjustments to 12.5, 25, 37.5, or 50 mg, and dose interruptions were based on individual platelet response in order to maintain platelet counts between 50,000 and 200,000/μL. An alternate-day dosing schedule (e.g., 12.5 mg and 25 mg on alternating days or 12.5 mg every other day) was allowed only if a once-daily dosing schedule of 12.5, 25, 37.5, or 50 mg was not appropriate to maintain the platelet count between 50,000 and 200,000/μL. Concomitant ITP treatment could

be reduced or interrupted at any time during the study per the investigator's discretion. Platelet counts were monitored weekly for the first 4 weeks and when the doses of study medication or concomitant medication were adjusted; otherwise, platelet counts were monitored every 4 weeks. The use of rescue treatments—defined as a new ITP medication, increased dose of a concomitant medication from baseline, platelet transfusion, or splenectomy—was allowed at any time during the study.

Evaluations

The primary evaluations were safety and tolerability of long-term treatment with eltrombopag in Japanese patients with chronic ITP. The severity and causality of AEs and drug-related AEs were assessed by the individual investigator and were summarized by frequency of occurrence and severity. AEs were considered serious when they were fatal, life-threatening, required hospitalization or prolongation of existing hospitalization, or resulted in disability/incapacity. Renal assessments and ophthalmologic examinations for cataracts were performed regularly during the study. Bone marrow biopsies were performed every 12 months while on treatment for patients who provided consent in order to assess the potential increase of reticulin fibers, but not done at baseline (before starting eltrombopag treatment). Fibrosis was graded by the investigator using the European consensus on grading bone marrow [16]. Assessments of efficacy included median platelet counts at each assessment, the proportion of patients with any bleeding episodes, the proportion of patients who reduced or discontinued the use of baseline ITP medications, and the use of rescue treatment. The severity of bleeding episodes was not assessed.

Analyses

Based on the number of patients planned for the previous 6-month Japanese study, 22 patients were expected to participate in the extension study. Descriptive statistics and frequency tables were used to summarize demographics, baseline characteristics, and safety and efficacy data. Patients receiving eltrombopag at any dose level were pooled for safety and efficacy analyses.

Results

Of the 23 patients enrolled in the previous 6-month eltrombopag study [15], 19 patients from 6 centers were enrolled in this extension study between May 2008 and February 2011. The primary evaluations of this study were safety and tolerability of long-term treatment with eltrombopag in Japanese patients with chronic ITP. All patients received at least one dose of eltrombopag. Four patients (21 %) withdrew from the study: 3 due to lack of efficacy and 1 due to a sustained platelet count above the level for hemorrhagic risk (50,000/μL) without eltrombopag treatment. The mean daily dose was 35.4 mg (Fig. 1). The median duration of exposure was 27.5 months (range 9.9–32.3 months), with 15 patients (79 %) treated for more than 2 years. Ten patients (53 %) required a dosing other than once daily to maintain the platelet count at the desired level (50,000–200,000/μL); 9 of these 10 patients (90 %) received 2 different doses on alternate days, and 3 patients received 12.5 mg once every 2, 6, or 7 days.

Baseline demographics and clinical characteristics are shown in Table 1. The median age was 61 years (range 27–73 years), and 63 % were female. At baseline, 15 patients (79 %) were receiving concomitant ITP medications, and 74 % had been splenectomized. Corticosteroids were the most common concomitant ITP medications (14/15). Fourteen patients (74 %) had baseline platelet counts <30,000/μL; the other 5 patients had baseline platelet counts ≥30,000/μL, including 1 patient with a count >50,000/μL.

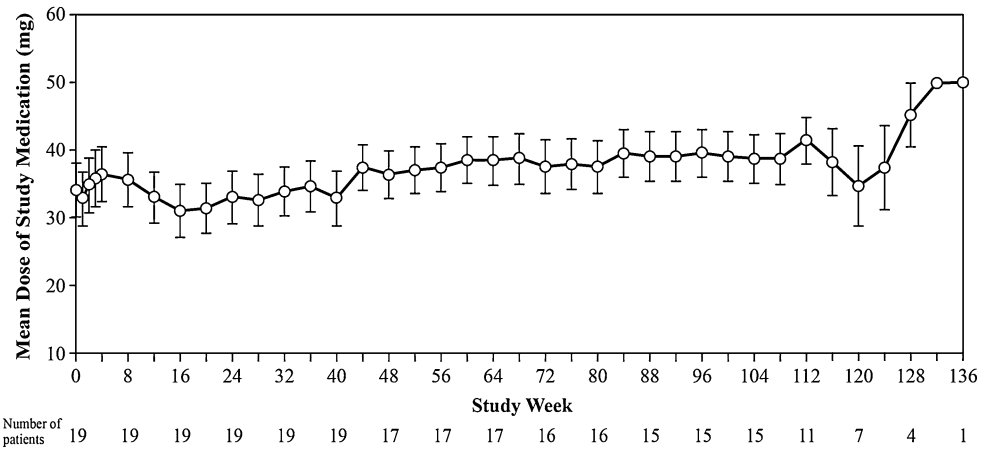

Fig. 1 Mean daily dose of eltrombopag by week. *Vertical bars* indicate standard deviation. Data shown do not include all assessments; the time points included here illustrate mean doses for the first several weeks of treatment and then at regular intervals thereafter. Patients enrolled in the study at different time points and consequently have differing assessment schedules; therefore, not all patients in study were assessed during each assessment shown

Table 1 Baseline demographics and clinical characteristics

Characteristic	Eltrombopag ($n = 19$)
Median age, years (range)	61 (27–73)
Sex, *n* (%)	
Female	12 (63)
Male	7 (37)
Race/ethnicity, *n* (%)	
Japanese	19 (100)
Concomitant ITP medication at baseline, *n* (%)	15 (79)
Splenectomized at baseline, *n* (%)	14 (74)
Platelet count at baseline, *n* (%)	
<30,000/μL	14 (74)
30,000–50,000/μL	4 (21)
>50,000/μL	1 (5)

Table 2 Adverse events reported during treatment

Preferred term	Eltrombopag ($n = 19$)
Patients with any adverse event, *n* (*n* related to study drug)[a]	19 (5)
Nasopharyngitis	12 (0)
Headache	4 (1)
Bronchitis	3 (0)
Diarrhea	3 (0)
Eczema	3 (0)
Insomnia	3 (1)
Iron deficiency anemia	3 (0)
Myalgia	3 (0)
Anemia	2 (0)
AST increased	2 (0)
Chest pain	2 (2)
Compression fracture	2 (0)
Cystitis	2 (0)
Fatigue	2 (0)
Hypertension	2 (0)
Influenza	2 (0)
Oropharyngeal pain	2 (0)
Pyrexia	2 (0)
Tenosynovitis	2 (0)
Cataract	1 (1)
Worsening of ITP	1 (1)
Serious adverse events	
Cataract	2 (2)

AST aspartate aminotransferase, *ITP* immune thrombocytopenia

[a] Events shown are those that occurred in 2 or more patients during treatment or considered related to eltrombopag treatment. The numbers of patients having adverse events considered by the investigator to be drug-related are shown in parentheses

Safety

AEs were reported for all patients while on treatment, with the majority being mild or moderate (Table 2). The most frequent AEs reported were nasopharyngitis (12 patients, 63 %) and headache (4 patients, 21 %). Eight AEs reported in 5 patients were considered by investigators to be related to eltrombopag treatment. Two events of chest pain (considered to be related to eltrombopag treatment) were reported in 2 patients; both had normal ECGs, and no sign of cardiovascular disease or thromboembolic event were observed at the time of onset.

Four events of cataract progression were reported in 3 patients during treatment; 3 events in 2 patients were considered by the investigator to be related to eltrombopag treatment. Of these 3 patients, 2 experienced a serious AE (SAE) due to hospitalization for cataract surgery; both patients had resolution after surgery. One patient was a 54-year-old female patient who had a steroid-induced cataract at baseline. She was treated with corticosteroids for about 10 years and experienced the AE 86 days after starting eltrombopag in this study. The other patient was a 62-year-old female patient who had a cataract at baseline and was treated with 10 mg of corticosteroids for at least 1 year. She experienced the AE on day 77. The investigators considered these events to be related to the corticosteroid therapy, but they could not discard the possibility of eltrombopag involvement. Eltrombopag was continued without cessation per the investigator's decision as it was judged that eltrombopag provided a clinical benefit over the risk of cataract progression.

A total of 9 SAEs were reported in 6 patients, including the 2 events of cataract progression described previously and 1 event each of abdominal pain, Mallory-Weiss syndrome, lumbar spinal stenosis, osteonecrosis, spinal osteoarthritis, cystitis-like symptoms, and menorrhagia. Other than the 2 events of cataract progression, all SAEs were considered by the investigator to be unrelated to eltrombopag treatment. All other drug-related AEs resolved without adjusting the dose of eltrombopag, with 1 exception. One patient had a worsening of ITP due to the lack of efficacy. This AE resolved after the discontinuation of eltrombopag and the use of rescue treatment (corticosteroids and intravenous immunoglobulin, followed by platelet transfusion and splenectomy).

No thromboembolic events occurred during or after long-term treatment with eltrombopag. Five patients experienced hepatobiliary laboratory abnormalities on treatment or within 30 days posttreatment, including: increases in the concentration of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or both to ≥3 times the upper limit of normal (ULN) in 3 patients; increases in alkaline phosphatase concentration to ≥1.5

times the ULN in 2 patients; and an increase in total bilirubin concentration to ≥1.5 times the ULN in 1 patient. These abnormalities resolved without dose adjustment. Of these abnormalities, the increase in ALT or AST concentration occurred in 1 patient each and was reported as an AE by the investigator. Additionally, increased AST was reported as an AE in another patient and resolved without dose adjustment.

Ten bone marrow biopsy samples were collected from 7 patients (3 patients had 2 biopsies each) treated with eltrombopag for more than 12 months. All biopsies were reported as normal or showing grade 1 bone marrow fibrosis (defined as the loose network of reticulin with many intersections, especially in perivascular areas). For the 3 patients who had 2 biopsies each, no clinically relevant change in bone marrow findings was seen (no changes in 2 patients; change from grade 1 to normal for 1 patient).

Efficacy

Median platelet counts began to increase after 1 week of treatment and remained elevated above 50,000/μL through most assessment visits after week 2 (Fig. 2). Three patients required <12.5 mg eltrombopag daily in order to maintain platelet counts at the desired range. Of these 3 patients, 2 patients subsequently maintained platelet counts above the level for hemorrhagic risk (>50,000/μL) without treatment with eltrombopag for at least 6 months. Three patients who had received concomitant corticosteroids throughout the study were withdrawn due to lack of efficacy after 108, 69, and 48 weeks, respectively, after starting treatment with eltrombopag in this study.

At baseline, 63 % (12/19) of patients experienced any bleeding episodes. The proportion of patients with any bleeding symptoms decreased to 21 % (4/19) after 2 weeks of treatment and remained lower than the baseline level throughout the study (Fig. 3).

Of the 15 patients receiving concomitant ITP medications at baseline, 10 patients permanently discontinued or had a sustained reduction (≥4 weeks) without receiving rescue treatment. Of these 10 patients, 8 patients maintained this reduction for ≥1 year, and 5 patients maintained this reduction for ≥2 years. Five of these 10 patients completely discontinued at least 1 baseline ITP medication.

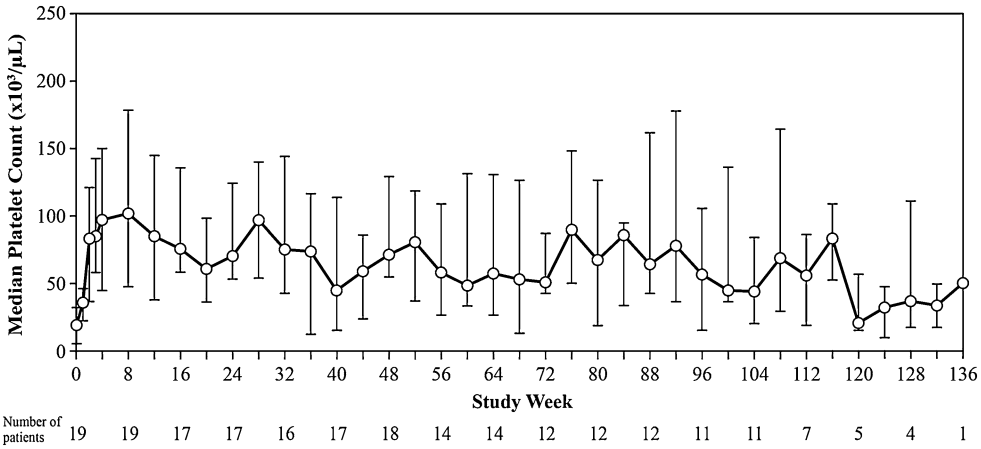

Fig. 2 Median platelet counts by week. *Vertical bars* indicate interquartile range. Data shown do not include all assessments; the time points included here illustrate median platelet counts for the first several weeks of treatment and then at regular intervals therefter. Patients enrolled in the study at different time points and consequently have differing assessments schedules; therefore, not all patients in study were assessed during each assessment shown

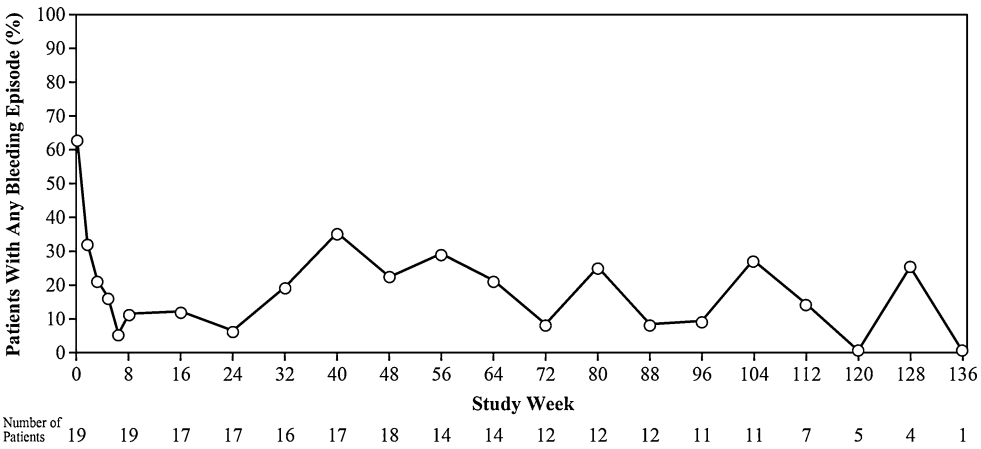

Fig. 3 Proportion of patients reporting any bleeding episode by week. Data shown do not include all assessments; the time points included here illustrate the percentage of patients with any bleeding episodes during the first several weeks of treatment and then at regular intervals thereafter. Patients enrolled in the study at different time points and consequently have differing assessment schedules; therefore, not all patients in study were assessed during each assessment shown

Five patients required rescue treatment during the study; after the end of eltrombopag treatment, one of these patients required a dose increase of corticosteroids, and one required corticosteroids, intravenous immunoglobulin, platelet transfusion, and splenectomy.

Discussion

We evaluated the long-term safety, tolerability, and efficacy of eltrombopag in Japanese patients with previously treated chronic ITP. The results show that eltrombopag was well tolerated, and no new safety concerns emerged with long-term administration. Eltrombopag increased platelet counts to ≥50,000/μL in >80 % of patients, reduced the number of bleeding episodes, and reduced the use of concomitant medications without requiring rescue medications. These improvements were maintained up to at least 3 years with eltrombopag doses of 12.5 to 50 mg daily. These results are similar to those observed in the previous Japanese study in which 69.6 % of patients achieved a platelet count ≥50,000/μL following 6 months of treatment with eltrombopag doses between 12.5 and 50 mg [15]. A similar platelet response was observed in placebo-controlled trials [17–19] and the long-term EXTEND study [20].

The starting dose for patients in this study was the last dose they received in the previous Japanese study, which was considered appropriate to achieve a response in the individual patient. A more rapid increase in platelet counts was observed compared with the previous Japanese study, for which the dose had been escalated from a lower starting dose. In addition, in some patients, a rapid increase in platelet counts, within a week of administering eltrombopag, was observed. These results confirm the findings from the previous study that a low starting dose with a gradual increase is appropriate for Japanese patients [15].

The AE profile of eltrombopag was similar to that reported in the previous study in Japanese patients [15] and in recent studies of eltrombopag in non-Japanese patients [19, 20]. Most AEs reported were mild or moderate in severity, and no thromboembolic events had been observed. Increases in aminotransferase levels were reported in this study, as well as in previous eltrombopag studies. Therefore, hepatic enzymes should be monitored before and during treatment with eltrombopag. Patients with chronic ITP generally have multiple risk factors for cataract, including older age and long-term corticosteroid use. In this study, 4 events of cataract progression were observed in 3 patients; all had cataracts before starting eltrombopag treatment and received long-term concomitant prednisolone. To date, there has been no evidence of an increased risk for cataracts or cataract progression caused by eltrombopag. While we cannot deny the possibility of cataract exacerbation being related to treatment with eltrombopag, regular ocular examination is recommended for patients with cataracts or risk factors of developing cataracts.

It has been demonstrated that reticulin fibers can be increased in the bone marrow of patients with various conditions, including autoimmune diseases, such as ITP [21]. In addition, there is a concern that chronic stimulation of megakaryocytes with TPO-R agonists may further increase reticulin or collagen fibers in the bone marrow, resulting in myelofibrosis. In this study, 7 patients underwent annual bone marrow biopsies while on study; none of the patients showed clinical symptoms typically associated with bone marrow abnormalities, which is consistent with recently reported results from the EXTEND study, a global, multicenter, open-label extension study of eltrombopag [22]. However, further evaluation of the long-term effect of eltrombopag on bone marrow fibers is warranted.

A clinical benefit of increased platelet counts is a reduction in the risk of bleeding. In this study, a rapid reduction in bleeding episodes was observed during treatment with eltrombopag and was correlated with increases in platelet count. In addition, treatment with eltrombopag allowed 67 % of patients to discontinue at least 1 concomitant ITP medication (primarily corticosteroids) or to have a sustained dose reduction; more than one-third of patients permanently discontinued at least 1 concomitant ITP medication. Steroid-related side effects impose a substantial burden on patients, and therefore, reduction in corticosteroid use presumably contributed to improved quality of life for these patients [23, 24].

Ethnic differences in eltrombopag exposure have been reported previously. An analysis of the population pharmacokinetics of eltrombopag demonstrated AUC values 87 % higher for East Asian compared with non-Asian patients with chronic ITP [14]. In the present study, the same dose range and dose adjustment criteria were used as in the previous Japanese study from which patients were enrolled. The mean daily doses were similar in both studies—33.7 mg in the 6-month study and 35.4 mg in the extension study. Although this was lower than that seen in EXTEND, the ability of this lower mean daily dose of eltrombopag to maintain elevated platelet counts and reduce bleeding risk has been confirmed for this patient population.

Three patients were withdrawn from the study due to a lack of efficacy; all 3 were receiving 50 mg eltrombopag daily and corticosteroids at the time of study withdrawal. Of these patients, 2 patients did not always maintain platelet counts >50,000/μL when administered eltrombopag 50 mg daily in the previous study. This finding may suggest that the maximum dose (50 mg) used in both studies was insufficient to increase the platelet counts in

these patients. However, for these patients, it should be considered whether treatment should continue, as frequency of bleeding episodes may be reduced even when platelet counts are <50,000/μL. In contrast, it is noteworthy that 2 patients maintained platelet counts >50,000/μL after cessation of eltrombopag in the absence of other ITP medications (e.g., corticosteroids). No bleeding episodes were observed in these patients during the study. Similar findings have also been reported in previous studies of romiplostim, another TPO-R agonist [25]. It has been reported that reduced levels and impaired immunosuppressive function of $CD4^+CD25^+$ regulatory T cells (Tregs) may contribute to the loss of immunologic self-tolerance in patients with ITP [26]. Recently, Bao et al. [27] reported an increase in Treg activity in patients with ITP treated with thrombopoietic agents and suggested that the increased Treg activity may be responsible for the sustained response seen with these treatments, although spontaneous remission cannot be ruled out as an explanation. Thus, eltrombopag discontinuation may be considered if the platelet count is stabilized at a high level when administering with a low dose of eltrombopag.

In conclusion, treatment with eltrombopag 12.5 to 50 mg for up to 3 years was safe and generally well tolerated in Japanese patients with previously treated chronic ITP, even for patients refractory to splenectomy. Long-term treatment with eltrombopag led to a sustained elevation of platelet counts, lowered the bleeding risk, and reduced the use of concomitant medications, including steroids. Eltrombopag is efficacious and safe as third-line therapy for patients who were refractory or intolerant to first- and second-line therapies.

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