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ORIGINAL ARTICLE

A phase 3b, multicenter, open-label extension study of the long-term safety of anagrelide in Japanese adults with essential thrombocythemia

Yuzuru Kanakura[1] · Yukari Shirasugi[2] · Hiroki Yamaguchi[3] · Michiaki Koike[4] · Takaaki Chou[5] · Shinichiro Okamoto[6] · Heinrich Achenbach[7] · Jingyang Wu[8] · Chiaki Nakaseko[9,10]

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Abstract

Cytoreductive therapy is used in high-risk essential thrombocythemia (ET) to reduce risk of thrombohemorrhagic complications. Anagrelide is an orally active, quinazolone-derived platelet-lowering agent approved for first-line treatment of high-risk ET in Japan. Long-term safety and efficacy data were collected from 53 Japanese high-risk ET patients (Study 308); 41 patients who completed Study 308 entered this phase 3b, open-label extension (Study 309; NCT01467661). Reductions in mean platelet counts occurred throughout the study, from 1021.6×10^9/L (at Study 308 baseline) to 675.4×10^9/L at final assessment. At month 48 (since Study 308 enrollment), mean platelet count was 444.5×10^9/L in the 10 patients who completed 4 years of therapy. Overall, platelet counts decreased from 1088.3×10^9/L at Study 308 baseline ($n=33$) to 473.5×10^9/L at final assessment ($n=31$). Long-term platelet count reductions were maintained without marked changes in mean anagrelide dose. Anagrelide was generally well tolerated, with anemia (54.7%) and headache (49.1%) as the most frequent adverse events. These findings indicate that anagrelide effectively reduces platelet counts in high-risk Japanese ET patients, with titration resulting in a well-tolerated, effective and sustainable dose. In conclusion, these results support anagrelide administration to high-risk Japanese ET patients using individualized dosing strategies defined in instructions previously approved in Europe and the USA.

Keywords Anagrelide · Essential thrombocythemia · Japan

Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by excess production of platelets [1–4]. The aim of treatment is to reduce the incidence of thrombohemorrhagic complications with cytoreductive therapy (CRT) indicated for patients at high risk of such events [5]. At present, two CRT treatments are licensed for the management of high-risk ET in Japan: hydroxycarbamide (HC) and anagrelide (Xagrid®, Shire Pharmaceutical Contracts Limited, Basingstoke, UK). HC is indicated for first-line treatment of high-risk ET and is the most widely used CRT [6], although it has been suggested that long-term

Study carried out at: Department of Hematology and Oncology, Osaka University Graduate School of Medicine, C9, 2-2, Yamada-oka, Suita, Osaka 565-0871, Japan.

✉ Yuzuru Kanakura
kanakura@bldon.med.osaka-u.ac.jp

1 Graduate School of Medicine, Osaka University, Osaka University Hospital, C9, 2-2, Yamada-oka, Suita, Osaka 565-0871, Japan

2 Tokai University School of Medicine, Isehara, Japan

3 Department of Hematology, Nippon Medical School, Tokyo, Japan

4 Juntendo University Shizuoka Hospital, Shizuoka, Japan

5 Niigata Cancer Center Hospital, Niigata, Japan

6 Keio University Hospital, Tokyo, Japan

7 Research & Development, Shire GmbH, Zug, Switzerland

8 Global Biometrics, Shire Pharmaceuticals, Lexington, MA, USA

9 Chiba University Hospital, Chiba, Japan

10 International University of Health and Welfare School of Medicine, Narita, Japan

use is associated with a higher incidence of secondary leukemia [7]. Anagrelide is an orally active, quinazolone-derived platelet-lowering agent indicated in Europe for the reduction of platelet counts in at-risk ET patients whose current therapy is not successful. Approval as a first-line treatment of high-risk ET was granted in Japan after completion of Study 308, which showed that anagrelide reduced platelet counts in high-risk Japanese patients with ET who were intolerant or refractory to their previous CRT, and that the safety profile was consistent with that described in European and US prescribing information [8].

Herein, we describe the long-term safety and efficacy of anagrelide in Japanese patients enrolled in Study 309, an extension to Study 308. The primary objective was to assess long-term safety of anagrelide in Japanese patients with ET, while secondary objectives were to evaluate long-term efficacy in Japanese adults (change in platelet count from baseline) and efficacy of dosing for the duration of exposure.

Methods

Study design

Study 309 was a phase 3b, open-label, extension study. Patients were enrolled in the extension if they completed the 12 months of Study 308 [8]. Marketing approval for anagrelide was granted in Japan while Study 309 was being conducted, and the study continued as a post-approval clinical study until anagrelide became commercially available. The first patient was enrolled in Study 308 in October 2010; Study 309 concluded in May 2015. Patients were enrolled in Study 308 from 18 sites in Japan, with patients from 16 sites continuing in Study 309. The study was registered with ClinicalTrials.gov with the identifier NCT01467661.

Patients

Complete inclusion and exclusion criteria for enrollment in Study 308 have been described previously [8]. In brief, Japanese patients ≥ 20 years of age were enrolled if they had high-risk ET and were refractory to or intolerant of first-line treatment. Patients were enrolled into Study 309 if they completed Study 308. Female patients were required to be post-menopausal, surgically sterile or using an acceptable method of contraception; there were no specific requirements for male contraception. Patients were excluded from the study if the investigator judged that it was not in the patient's best interest to continue receiving anagrelide. All patients gave written, informed and dated consent to participate in the original study and the extension, which were designed and conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice.

Treatment

During Study 308, patients received anagrelide at an initial dose of 0.5 mg twice daily by oral administration, as described previously [8]. The initial dose was maintained for at least 1 week before titration, on an individual basis, to achieve and maintain an adequate platelet count response ($< 600 \times 10^9$/L) at the lowest effective dose. Titration increments could not exceed 0.5 mg/day in 1 week, and total daily doses could not exceed 10 mg. Single doses could not exceed 2.5 mg, and patients could receive up to four doses per day. In Study 309, each patient received anagrelide at an initial dose equal to that received at the end of Study 308. The dose of anagrelide was adjusted upward or downward to maximize efficacy and tolerability according to the titration rules described for Study 308 above.

Use of aspirin was permitted during the study. Anticoagulant therapies (e.g., warfarin, heparin and heparin analogs), phosphodiesterase 3 inhibitors, and other cytoreductive therapies were not permitted.

Assessments

The primary objective of the study was to assess the safety of long-term anagrelide use in Japanese patients with ET. Safety was assessed by general questioning of study participants to identify adverse events (AEs) at the initial visit, quarterly visits and at the patient's final visit. Data from Study 308 were electronically transferred and ongoing AEs were recorded for Study 309. For each AE, the investigator determined severity, seriousness and the likely relationship to anagrelide. AEs were considered mild if they were usually transient and required only minimal treatment or therapeutic intervention, as moderate if they were usually alleviated with specific therapeutic intervention, and as severe if they interrupted usual activities of daily living, significantly affected clinical status or required intensive therapeutic intervention. Physical examinations, electrocardiograms (ECGs), vital signs and laboratory tests were evaluated at all study visits. AEs were coded using version 15.1 of the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events (TEAEs) were summarized and presented by system organ class and preferred term for all TEAEs (as assessed by the investigator), and by maximum severity. Treatment-emergent serious adverse events (SAEs) and AEs leading to withdrawal were also assessed.

Efficacy was evaluated using absolute values and changes from baseline in platelet count, as a secondary objective of the study. Platelet counts were recorded as part of the clinical laboratory assessments.

Statistical analysis

The safety analysis set was defined as all patients who had taken at least one dose of anagrelide since enrollment into Study 308 and is the primary focus of this manuscript. The post-approval analysis set was defined as all patients included in the safety analysis set who continued into the post-approval part of Study 309 ($n = 33$). All analyses were conducted within both the safety analysis set and the post-approval analysis set. Descriptive statistics were used to summarize platelet count and change from baseline in platelet count, where baseline was defined as the baseline for Study 308. Mean platelet count data (with 95% confidence intervals) at scheduled visits, and the average dispensed daily dose of anagrelide, were also presented graphically over time using scatter plots. The proportion of subjects (and two-sided 95% confidence intervals) with platelet counts $< 600 \times 10^9$/L was determined for each scheduled visit. The final assessment visit included data from assessments made at the end of study visit in Study 309, the early termination visit from either Study 308 or Study 309, or from the last available scheduled visit. Unscheduled or titration visit data were not used.

Results

Patient disposition, baseline characteristics and treatment exposure

Study 308 was completed by 42 of the 53 enrolled patients, 41 of whom continued into Study 309 (Fig. 1). Thirty-two of 41 patients completed Study 309 and 9 patients discontinued prematurely. Reasons for discontinuation during either Study 308 or 309 included AEs (16 patients, 30.2%), lack of efficacy (3 patients, 5.7%), and subject withdrawal (1 patient, 1.9%). Across Studies 308 and 309, 44 patients (83.0%) attended the baseline visit, 42 (79.2%) completed at least 6 months, 41 (77.4%) at least 12 months, 39 (73.6%) at least 18 months, 37 (69.8%) at least 24 months, 36 (67.9%) at least 30 months, 26 (49.1%) at least 36 months and 12 (22.6%) at least 42 months. To analyze long-term safety and efficacy in this patient population, the majority of the results discussed below concern all patients who participated in Study 308 ($n = 53$) from the first dose in Study 308 until the final dose in either Study 308 or 309.

The baseline characteristics of patients enrolled in Study 308 (i.e., the safety analysis set) have been described previously [8]. The study population comprised 30 women (56.6%) and 23 men (43.4%) with a median age of 66.0 years (range 36–86 years). Thirty-four patients (64.2%) were intolerant of their previous or current CRT, while 19 patients

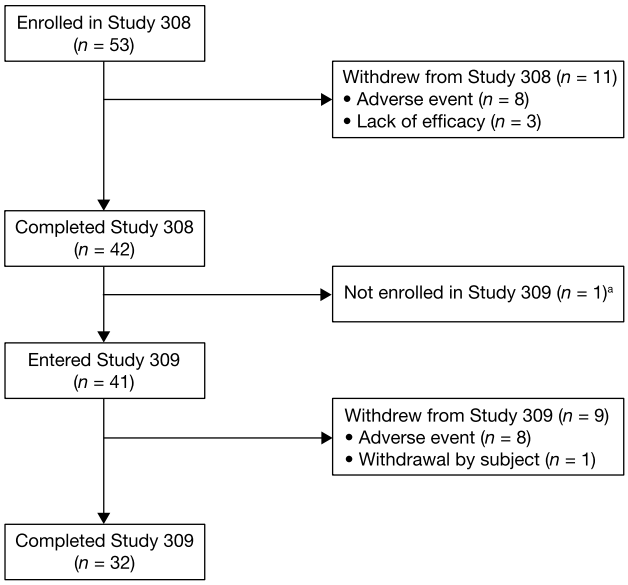

Fig. 1 Patient disposition

(35.8%) were refractory. Thirty-five patients (66.0%) received concomitant aspirin.

For the safety analysis set, the median duration of exposure to anagrelide was 1261 days (range 13–1544 days), with a median total dose of 1.76 g (range 0.02–6.58 g). The median daily dose of anagrelide was 1.80 mg/day (range 0.73–4.84 mg/day; mean 2.09 mg/day) (Table 1). Changes in dose were infrequent during Study 309 and the majority of patients (75.4%) had a final daily dose of 1.0–3.0 mg/day, with doses generally remaining stable after the first 3 months. Exposure was similar in the post-approval part of the study, with a median average daily dose of 1.86 mg/day and the majority of patients receiving a final dose of 1.0–3.0 mg/day.

Efficacy

Platelet counts were reduced during treatment with anagrelide, with sustained reductions throughout the study period (Fig. 2). Mean platelet counts decreased throughout the study, from 1021.6×10^9/L at Study 308 baseline in 53 subjects, to 675.4×10^9/L at final assessment. In the ten patients who reached month 48 (the primary final analysis for those still on treatment) in Study 309, the mean platelet count was 444.5×10^9/L (a reduction of 822.5×10^9/L from baseline). Sustained reductions in platelet count were also noted among patients who entered the post-approval phase of the study. In the post-approval analysis set, platelet count decreased from a mean of 1088.3×10^9/L at Study 308 baseline ($n = 33$) to 473.5×10^9/L at final assessment ($n = 31$). Long-term reductions in mean platelet count were

Table 1 Anagrelide exposure (safety analysis set)

	Anagrelide ($n=53$)
Length of exposure, days	
Mean (SD)	1027.6 (545.57)
Median (range)	1261.0 (13–1544)
Total dose, g	
Mean (SD)	2.18 (1.723)
Median (range)	1.76 (0.02–6.58)
Average daily dose, mg/day	
Mean (SD)	2.09 (1.037)
Median (range)	1.80 (0.73–4.84)
Length of exposure category, *n* (%) (days)	
< 90	7 (13.2)
90 to < 180	2 (3.8)
180 to < 270	1 (1.9)
270 to < 360	2 (3.8)
360 to < 450	0
450 to < 540	0
540 to < 630	1 (1.9)
630 to < 720	1 (1.9)
720 to < 810	1 (1.9)
810 to < 900	1 (1.9)
900 to < 990	2 (3.8)
990 to < 1080	1 (1.9)
1080 to < 1170	2 (3.8)
1170 to < 1260	3 (5.7)
1260 to < 1350	7 (13.2)
1350 to < 1440	8 (15.1)
1440 to < 1530	7 (13.2)
1530 to < 1620	7 (13.2)

SD standard deviation

maintained without marked changes in the mean dose of anagrelide (Fig. 2).

At month 12, 41 patients had available platelet counts. At baseline, 37 of those 41 patients had a platelet count of $\geq 600\times10^9$/L, and 4 patients had a platelet count of $<600\times10^9$/L. Of the 37 patients who had a platelet count of $\geq 600\times10^9$/L at baseline, 26 patients shifted to $<600\times10^9$/L at month 12. At month 24, of the 34 patients who had a platelet count of $\geq 600\times10^9$/L at baseline, 27 shifted to $<600\times10^9$/L. At month 36, of the 32 patients who had a platelet count of $\geq 600\times10^9$/L at baseline, 26 shifted to $<600\times10^9$/L. At the final assessment, of the 47 patients who had platelet counts of $\geq 600\times10^9$/L at baseline, 27 had shifted to $<600\times10^9$/L. A summary of all patients in the full safety analysis set who had a platelet count of $<600\times10^9$/L at each assessment is presented in Fig. 3.

Safety

All 53 patients had at least one treatment-emergent AE (TEAE), and the majority (92.5%) had a TEAE that was assessed by the investigator as being related to anagrelide (Table 2). The most frequent TEAEs were anemia, headache, nasopharyngitis, palpitations, diarrhea, peripheral edema, hypertension, fatigue and pyrexia (Table 2). Eleven patients developed neoplasms (20.8%, exposure-adjusted incidence rate: 7.32 per 100 patient-years). Of these, four patients (7.5%) developed myelofibrosis (exposure-adjusted incidence rate: 2.66 per 100 patient-years). TEAEs were mild (24.5%) or moderate (54.7%) in most patients. Serious TEAEs occurred in 21 patients (39.6%) in the safety analysis set, including two fatalities (one due to cardiac failure and one to cerebral hemorrhage). No individual serious TEAE occurred in more than two patients. Eleven patients (20.8%)

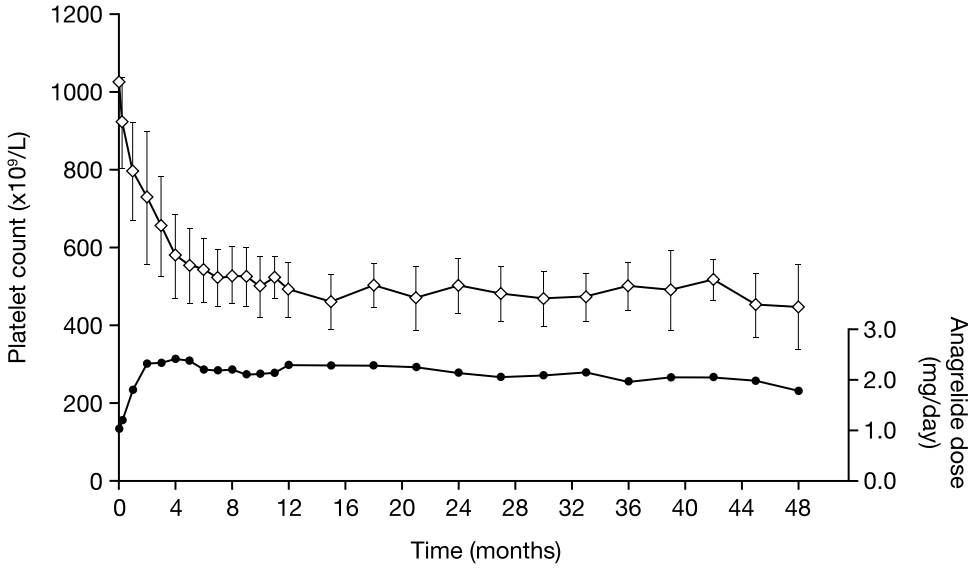

Fig. 2 Mean platelet counts (and 95% confidence intervals) and mean anagrelide dose over time (safety analysis set)

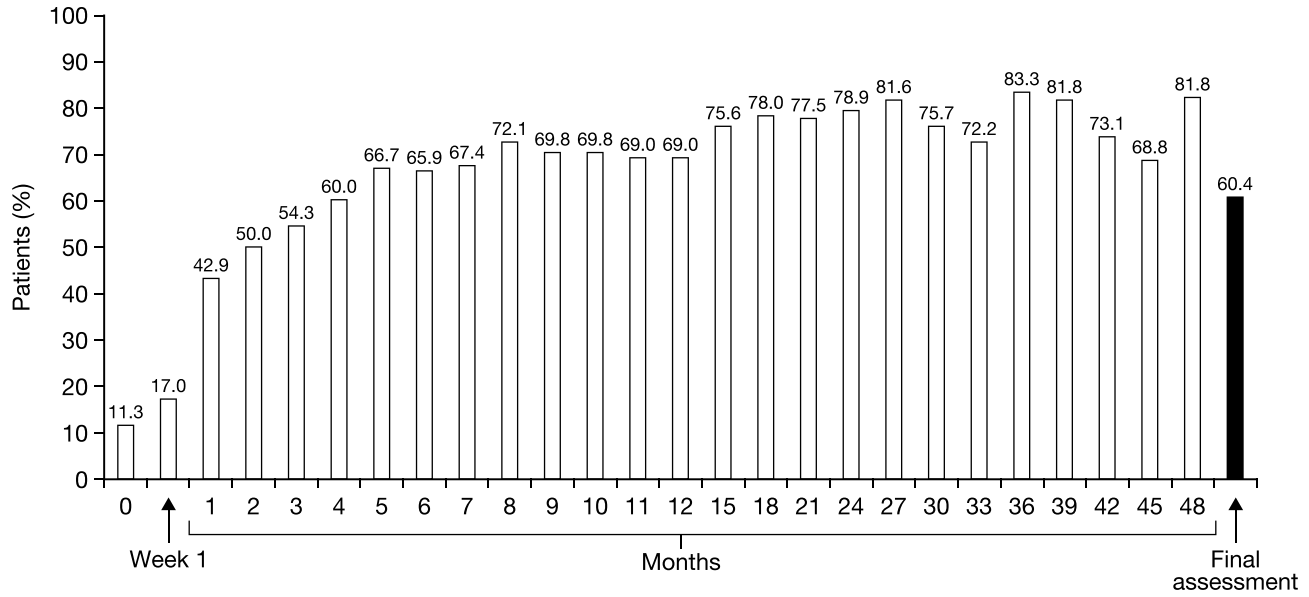

Fig. 3 Percentage of patients achieving a platelet count of $< 600 \times 10^9$/L over time (safety analysis set)

had a severe TEAE, with cerebral hemorrhage and headache each occurring in two individuals, and other severe TEAEs in no more than one patient. During the post-approval part of the study there were no severe TEAEs, and moderate TEAEs in only four patients. In the safety analysis set, 16 patients (30.2%) had a total of 24 TEAEs that led to dose discontinuation. Three patients (5.7%) had headache, 2 (3.8%) had palpitations and two (3.8%) had cerebral hemorrhage. All other TEAEs leading to discontinuation were observed in no more than one patient. Most TEAEs that led to drug discontinuation were mild or moderate in severity (17 of 24), and judged as treatment-related by investigators. More than two-thirds of TEAEs leading to discontinuation occurred within the first year of therapy (during Study 308), and 11 of 24 TEAEs that led to discontinuation occurred within the first 60 days. One patient was withdrawn due to a non-treatment-emergent AE.

Changes in laboratory parameters were generally consistent with those expected in ET patients who received anagrelide. TEAEs related to clinical laboratory results reported in more than 5% of patients in the safety analysis set were anemia (54.7%), iron deficiency anemia (11.3%), eosinophilia (7.5%), abnormal hepatic function (9.4%), hyperuricemia (15.1%) and thrombocytopenia (5.7%), with most events rated as mild in severity. Anemia was classified by the investigator as related to anagrelide in 26 patients (49.1%); there were no cases of severe or serious anemia. Twenty-six patients (49.1%) had a hemoglobin level below the lower limit of normal at baseline. Mean hemoglobin levels decreased slightly during the study, from 121.3 g/L at baseline to 108.2 g/L at the final assessment. Mean white blood cell (WBC) counts increased slightly over the study period from 8.38×10^9/L at baseline to 14.78×10^9/L at final assessment. There were increases in mean alkaline phosphatase and gamma-glutamyl transferase (GGT) levels, although elevations above the normal ranges did not occur in all affected patients; elevations above the normal range generally occurred in isolation with no clear association with abnormalities in other hepatic enzymes. No discernible changes in urinalysis variables were noted.

With the exception of mild increases in heart rate, there were no clinically relevant changes from baseline in vital signs or weight. Abnormalities in ECG or echocardiogram results were generally transient. Three patients had QT prolongation.

Discussion

In this phase 3b, multicenter, open-label, extension study, anagrelide was associated with sustained reductions in platelet counts among Japanese patients who were refractory to or intolerant of their current CRT. The extension study demonstrated that the efficacy observed with anagrelide at 12 months in Study 308 was sustained long term. Overall, platelet count decreased from a mean of 1021.6×10^9/L at baseline in Study 308 to 675.4×10^9/L at the final assessment in Study 309 (median duration of exposure to anagrelide was 1261.0 days). For the ten patients who reached month 48, the mean platelet count was 444.5×10^9/L (a reduction of 822.5×10^9/L from baseline). These results from Japanese patients with ET are consistent with those seen in studies of ET patients in Europe, Australia and Singapore [9, 10].

Table 2 Adverse events

	Safety analysis set ($n=53$) Number (%)	Post-approval analysis set ($n=33$) Number (%)[a]
Patients with any TEAE	53 (100.0)	13 (39.4)
Serious TEAEs	21 (39.6)	1 (3.0)
Treatment-related TEAEs	49 (92.5)	1 (3.0)
TEAEs leading to dose discontinuation	16 (30.2)	0
AEs leading to death	2 (3.8)	0
Most frequent TEAEs (reported by ≥ 10% of patients in the safety analysis set)		
Anemia	29 (54.7)	0
Headache	26 (49.1)	0
Nasopharyngitis	22 (41.5)	2 (6.1)
Palpitations	21 (39.6)	0
Diarrhea	19 (35.8)	1 (3.0)
Edema peripheral	16 (30.2)	0
Hypertension	14 (26.4)	1 (3.0)
Fatigue	11 (20.8)	0
Pyrexia	11 (20.8)	0
Pain in extremity	10 (18.9)	2 (6.1)
Contusion	9 (17.0)	0
Abdominal pain upper	8 (15.1)	0
Gingival bleeding	8 (15.1)	0
Bronchitis	8 (15.1)	0
Arthralgia	8 (15.1)	0
Back pain	8 (15.1)	0
Dyspnea	8 (15.1)	0
Epistaxis	8 (15.1)	1 (3.0)
Hyperuricemia	8 (15.1)	0
Constipation	7 (13.2)	1 (3.0)
Gastroenteritis	7 (13.2)	0
URTI	7 (13.2)	0
Rash	7 (13.2)	1 (3.0)
GGT increased	7 (13.2)	0
Cerebral infarction	7 (13.2)	0
Renal impairment	7 (13.2)	0
Vertigo	7 (13.2)	0
Iron deficiency anemia	6 (11.3)	0
Dental caries	6 (11.3)	0
Nausea	6 (11.3)	0
Hypoesthesia	6 (11.3)	0
BAP increased	6 (11.3)	0
Dehydration	6 (11.3)	0

AE adverse event, *BAP* blood alkaline phosphatase, *GGT* gamma-glutamyltransferase, *TEAE* treatment-emergent adverse event, *URTI* upper respiratory tract infection

[a]Only TEAEs occurring after the start of the post-approval phase are reported for the post-approval analysis set

During Study 308 and extension (Study 309), anagrelide doses were titrated to maximize efficacy and tolerability. After the first 3 months of treatment, anagrelide doses generally remained stable with a median average daily dose of 1.80 mg/day (mean 2.09 mg/day), and the majority of patients received a final daily dose of 1.0–3.0 mg/day. Changes in dose were infrequent after the first 12 months of treatment. Similar results were obtained in the post-approval part of the study. The median average daily dose of approximately 1.8 mg/day in the present study was slightly higher than that reported in a long-term European study of anagrelide (1.5 mg/day) [11, 12], suggesting that lower doses may be used with increased experience with anagrelide therapy in Japan.

Anagrelide was well tolerated in Japanese patients with ET during this extension study, with most TEAEs being of mild (24.5%) or moderate (54.7%) severity. The most frequent TEAEs were anemia (54.7%) and headache (49.1%). The high incidence of anemia in the study, which was also noted during the original study [8], reflects a recognized and common adverse effect of anagrelide [13]. As previously noted [8], 45% of patients enrolled in Study 308 had a history of anemia, which may reflect the high incidence of diet-related iron deficiency observed within the Japanese population [14]. However, there was no serious anemia TEAEs during the studies and only one discontinuation due to anemia. The occurrence of anemia and low hemoglobin levels in Japanese patients enrolled in Studies 308 and 309 may be indicative of a high risk of disease progression and is consistent with the refractory nature of their condition [15, 16]. Other studies of anagrelide in non-Japanese patients have reported lower rates of anemia (8–9%) [9, 10]. While mild-to-moderate anemia was the most frequent TEAE, it is notable that leukocyte counts increased over the treatment period, consistent with previous studies suggesting that anagrelide primarily acts by selectively suppressing the differentiation of megakaryocytes, while sparing other lineages [17–21]. Four patients developed myelofibrosis during Study 308 and Study 309, with an event rate of 2.66 per 100 patient-years. This is higher than the rate of 0.61 per 100 patient-years found in patients who only received anagrelide in the recently published EXELS study [22]. A number of variables may have contributed to the difference in event rates reported in the two studies. The more rigorous AE reporting in the clinical trial compared with the observational EXELS study may have led to a higher number of reported cases of myelofibrosis. Additionally, the patient population studied differed between the studies as the much larger EXELS study ($n=3649$) enrolled both newly diagnosed and treatment-experienced patients, while in Study 308 and Study 309 only treatment-experienced patients who were intolerant or refractory to previous cytoreductive therapy were

included [8]. This could also have contributed to the different event rates for myelofibrosis.

With the exception of anemia, the frequency of other TEAEs was generally consistent with those encountered in non-Japanese patients. Of note, the frequency of headache, a common occurrence among patients with ET [23], was high in Studies 308 and 309 and consistent with previously reported data from a study of non-Japanese patients [9].

Overall, the results from Studies 308 and 309 indicate that anagrelide effectively reduces platelet counts in high-risk Japanese patients who are refractory to or cannot tolerate their current treatment. These results indicate that, within 3 months of initiating treatment, anagrelide can generally be titrated to achieve a well tolerated and effective dose that can be continued as part of long-term maintenance therapy. Consistent with the dosing instructions previously approved in Europe and the USA, our results confirm the feasibility of long-term administration of anagrelide to high-risk Japanese patients with ET, using an individualized dosing strategy.

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Compliance with ethical standards

Conflict of interest Yuzuru Kanakura: grants from Kyowa Hakko Kirin, Shionogi, Chugai Pharmaceutical, Pfizer, Eisai, Astellas, Nippon Shinyaku, Alexionpharma, Bristol-Myers Squibb, Toyama Chemical, and Fujimotoseiyaku. Yukari Shirasugi: honoraria from Novartis. Hiroki Yamaguchi: none. Michiaki Koike: none. Takaaki Chou: honoraria from Celgene, Novartis, Takeda, Bristol-Myers Squibb. Shinichiro Okamoto: none. Henri Achenbach: employed by Shire, stock or other interests in Shire. Jingyang Wu: employed by Shire, stock or other interests in Shire. Chiaki Nakaseko: none.

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