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ORIGINAL ARTICLE

Open-label, dose-titration and continuation study to assess efficacy, safety, and pharmacokinetics of anagrelide in treatment-naïve Japanese patients with essential thrombocythemia

Shinichiro Okamoto · Yoshitaka Miyakawa · Jonathan Smith · Ian Hodgson · Brihad Abhyankar · Steven Troy · Yuzuru Kanakura

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Abstract Although anagrelide is widely used for the treatment of essential thrombocythemia (ET) in the USA and Europe, it is not licensed in Japan. Existing literature has reported differences in polymorphism and activity of CYP1A2 in Japanese and non-Japanese ethnic groups, which may alter anagrelide metabolism. We intended to identify the optimum dosage of anagrelide in treatment-naïve Japanese patients with ET and assess its long-term safety and efficacy. Twelve patients with ET and a platelet count of $\geq 80 \times 10^4/\mu L$ were enrolled. Anagrelide was administered at an initial dose of 0.5 mg/day (weeks 1–4), then increased to 1.0 mg/day (weeks 5–8). During the following maintenance (weeks 9–52) and continuation periods (weeks 53–104), the dose was adjusted according to patient safety data and to maintain target platelet counts ($<60 \times 10^4/\mu L$). Increasing the dose led to a decrease in mean platelet count, and target platelet counts were maintained in 11 patients. Adverse events were mild or moderate, and none led to discontinuation. This cohort of Japanese patients exhibited higher pharmacokinetic exposures of anagrelide and its active metabolite than those previously documented in non-Japanese patients. These differences were modest, suggesting specific dosing regimens for Japanese patients are not required.

Keywords Essential thrombocythemia · Anagrelide · Japanese patients · Elevated platelet count · Pharmacokinetic profiles

S. Okamoto (✉) · Y. Miyakawa
School of Medicine, Keio University,
35 Shinanomachi, Shinjuku, Tokyo 160-8582, Japan
e-mail: okamoto@a7.keio.jp

J. Smith · I. Hodgson · B. Abhyankar
Shire Pharmaceutical Development Ltd., Basingstoke, UK

S. Troy
Shire Development LLC, Wayne, Pennsylvania, USA

Y. Kanakura
Osaka University Graduate School of Medicine, Osaka, Japan

Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized predominantly by thrombocytosis and abnormal megakaryocyte proliferation [1]. According to the World Health Organization (WHO), diagnosis of ET requires a sustained elevation in platelet count ($\geq 45 \times 10^4/\mu L$) and increased maturation and hyperplasia of megakaryocytes. In addition, diagnostic criteria for ET should not satisfy WHO criteria for any other myeloproliferative neoplasm [2]. Current therapy for ET is based on thrombotic risk, with patients stratified into low-, intermediate- and high-risk categories. Anti-aggregatory therapy, such as low-dose aspirin, is recommended for all patients with ET [3], and cytoreductive therapy is also indicated in high-risk patients in order to minimize the risk of thrombotic events and bleeding complications [4]. According to British [5] and European [3] guidelines, high-risk patients, characterized as having at least one of a platelet count $>150 \times 10^4/\mu L$, a history of thrombohemorrhagic events, or >60 years of age, are recommended for cytoreductive therapy.

In Japan, ranimustine is currently the only licensed treatment for patients with ET; however, a number of other cytoreductive therapies are available. Of these therapies, hydroxycarbamide has been widely used off-label for Japanese patients with ET, although treatment choices vary

significantly among hematologists in Japan [6]. In Europe, anagrelide is indicated for the reduction of elevated platelet counts in at-risk patients with ET who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy [7]. In the USA, anagrelide is indicated as first-line treatment for patients with thrombocythemia, secondary to myeloproliferative disorders, in order to reduce elevated platelet counts and the risk of thrombosis [8].

It has been shown that there are significant disparities in the polymorphism and activity of CYP1A2, a key enzyme metabolizing anagrelide, in patients of different ethnic backgrounds [9]. Tanaka and colleagues evaluated the pharmacokinetic (PK) profile of anagrelide in 26 healthy male Japanese volunteers (T. Tanaka, M. Ohtsuji, R. Urae; AGR-I-01-J Clinical Study Report, 2000), and compared these data to the PK profile of anagrelide in healthy non-Japanese volunteers (S. Milutinovic; SPD422-103 Clinical Study Report, 2003), with the findings suggesting that there are no clinically significant differences between the PK profiles of anagrelide in these populations.

The aims of our study were to identify the optimal dose and treatment schedule of anagrelide in Japanese patients with ET, and to further assess the long-term safety and efficacy profile of anagrelide. We also performed a compartmental analysis to compare the PK profiles of anagrelide and its active metabolite, 3-hydroxy anagrelide (BCH24426), in this cohort of Japanese patients, with the previously observed PK profiles of non-Japanese patients [10].

Materials and methods

Study design

Study KRN654-A03/A04 was a phase I/II multi-center, open-label, dose-titration study of anagrelide in Japanese patients with ET. The study comprised an initial dose evaluation period (weeks 1–8), followed by a maintenance dose evaluation period (weeks 9–52). A continuation period ensued for a further 52 weeks. Written, informed consent was obtained from all participants.

Participants

The rationale for the study sample size considered the 381 patients with ET that were identified from 40 surveyed medical institutions in a study reported by Dan et al. [6]. The investigators of the present study conducted a survey of patients at 28 medical institutions (the majority of which were the medical institutions selected in the study by Dan et al.) in order to assess the current treatment regimes and platelet counts of patients. Of the 567 patients with ET that were considered, 61 (11 %) had a platelet count exceeding $100 \times 10^4/\mu L$. Patients included in the present study would be required to attend a medical institution capable of assessing eligibility criteria and performing PK assessments. Thus, on feasibility, it was concluded that only one to two patients could be enrolled from each site, and a total sample size of eight patients was planned for this study.

Treatment-naïve patients aged 20–75 years having a confirmed diagnosis of ET, a platelet count of $\geq 100 \times 10^4/\mu L$ as determined over the 6-month period prior to enrollment, and a platelet count of $\geq 80 \times 10^4/\mu L$ in the pre-study tests were included in the study. Inclusion criteria for the continuation period were patients who had successfully completed the initial dose evaluation and maintenance dose evaluation periods, and for whom there was a clinical need to continue with anagrelide treatment. Patients with drug hypersensitivity, cardiac disease, hepatic or renal impairment and patients with a history of severe thrombosis or co-existing thrombosis, were excluded. Similarly, pregnant or nursing women, patients with a history of drug or alcohol abuse, and patients with a co-existing malignancy, or having taken an antineoplastic agent or interferon over the 12 weeks prior to enrollment, were also ineligible for inclusion. Exclusion criteria for the continuation period were defined as any patient who had suffered a serious adverse event (SAE) in the original evaluation periods.

Interventions

Anagrelide hydrochloride was administered as monotherapy in the form of a white, opaque hydroxypropyl methylcellulose (HPMC) capsule, containing 0.5 mg of active product. Combination therapy with hydroxycarbamide during the entirety of the study was not permitted. Over the initial dose evaluation period, 0.5 mg (one capsule) was taken daily during weeks 1–4, followed by a 0.5 mg dose taken twice daily (1.0 mg/day) during weeks 5–8. By week 9, if the target platelet count ($<60 \times 10^4/\mu L$) was not achieved, the anagrelide dose was increased in 0.5 mg/day increments until the target platelet count was reached. Thereafter, the dose was adjusted in accordance with the anagrelide dose adjustment schedule in the range of 0.5–6.0 mg/day, in order to maintain the platelets at the target level. The anagrelide dose adjustment schedule provided guidance for the study investigators to determine the required dosage and frequency of administration for each patient. Dependent on their current daily dose, patients were given an anagrelide dose of 0.5–2.0 mg (one to four capsules) up to three times a day, immediately after meals.

The anagrelide dose range of 0.5–6.0 mg/day was approved by the study investigators following amendments to the study protocol. Initially, the maximum dose was set at 4.0 mg/day, based on the rationale that a previous single-dose study of anagrelide in healthy Japanese adults had confirmed safety up to 2.0 mg/day, and that the number of doses per day was set at two. Upon starting the present study, it was anticipated that two patients would require a dose in excess of 4.0 mg/day in order to achieve the target platelet count. Thus, the study protocol was amended to allow for a new higher maximum dose of 6.0 mg/day. In accordance with the anagrelide dose adjustment schedule, the study investigators concluded that the maximum administrable dose of anagrelide during the dose evaluation period would not exceed 6.0 mg/day, with 0.5 mg/day incremental increases only being permitted every 2 weeks.

The continuation period began on the final day of tests in the original phase I/II study. During this period, the anagrelide dose adjustment schedule allowed for anagrelide to be administered in the extended range of 0.5–10 mg/day so as to maintain the target platelet count.

Throughout the study, safety and efficacy evaluations were performed. In order to perform a comprehensive assessment of PK data, a post-hoc compartmental analysis was conducted.

Endpoints

The primary endpoint of this study was changes in platelet count during the initial dose evaluation period (weeks 1–8). Secondary endpoints included changes in platelet count during the investigational product treatment period (weeks 1–52), and the percentage of patients achieving the target platelet count at week 52. Safety endpoints included all adverse events (AEs) recorded during the course of the study and the incidence of AEs related to thrombosis and hemorrhage.

Pharmacokinetic evaluation

Blood samples for PK analysis were collected into lithium heparin tubes and immediately chilled on ice. Following centrifugation of the samples at approximately 3,000 rpm for 10 min at 4 °C, the separated plasma was stored in a freezer below −20 °C until it was shipped to York Bioanalytical Solutions, York, UK, for plasma concentration analysis. Plasma concentrations of anagrelide, its active metabolite BCH24426 and its inactive metabolite 2-amino-5,6-dichloro-3,4,-dihydroquinazoline (RL603), were determined by liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) with a lower limit of quantification of 0.0929 ng/mL for anagrelide and 0.10 ng/mL for BCH24426 and RL603.

The plasma concentrations of anagrelide and its metabolites on day 1 and day 7 were described by a one-compartment PK model with first-order absorption and an absorption/input lag time. Changes in trough plasma concentrations of anagrelide and its metabolites during the maintenance dose evaluation period (weeks 9–52) were also measured.

Statistical methods

Descriptive statistics were calculated for changes in platelet count and for the target platelet count achievement rate, utilizing data collected from the initiation of the phase I/II study up until the final day of the continuation period. All 12 patients who received the investigational product were included in the safety analysis population. Safety analysis included assessment of all AEs and their incidence from the start of treatment until the tests prior to study closure. When any one patient had the same AE on more than one occasion, the incident with the greatest severity was considered. AEs related to the incidence of thrombosis and hemorrhage were also calculated. Summary statistics for PK parameters of anagrelide, BCH24426, and RL603 were calculated on day 1 and day 7. Log-linear graphs were plotted to summarize mean values and standard deviations of plasma concentrations of anagrelide and its metabolites on day 1 and day 7 of investigational product administration.

Results

Fourteen patients were enrolled, and in adherence with study inclusion and exclusion criteria, two patients were found to be ineligible for study participation as a result of their coexisting conditions. One patient had peptic ulceration and the other experienced an intramuscular hematoma, in addition to testing positive for hepatitis C virus antibody during the pre-study tests. Thus, these two patients were not treated with anagrelide (Fig. 1). The remaining 12 patients successfully completed the initial dose and maintenance dose evaluation periods and elected to continue receiving treatment during the continuation period (52 weeks). One patient was down-titrated to 0.5 mg/day following an AE experienced during the 1.0 mg/day treatment period.

All 12 patients were included in the full analysis set (FAS), per protocol set (PPS) and PK population. Following a review of the data handling rules, the data for the patient who was down-titrated between days 35 and 42 were excluded from the efficacy and PK analysis, beginning on the day of the deviation, and before PPS and PK analyses were conducted. The FAS population comprised

three male and nine female patients having a mean age of 48.2 years (20–39 years, $n = 4$; 40–59 years, $n = 7$; 60–74 years, $n = 1$). The majority of patients were non-smokers ($n = 11$).

Efficacy

The changes in platelet count during the initial dose evaluation period were measured in the PPS population. Changes in platelet count and target platelet count achievement rate during the entire anagrelide treatment period (weeks 1–52) were measured in the FAS population alone. At initial dose administration (day 1, 0.5 mg/day), mean platelet counts were $130.99 \pm 34.36 \times 10^4/\mu L$; the minimum and maximum platelet counts were $94.7 \times 10^4/\mu L$ and $198.9 \times 10^4/\mu L$, respectively. Increasing the dose to 1.0 mg/day at week 5, the mean platelet count (±standard deviation) reached $120.96 \pm 48.57 \times 10^4/\mu L$, and continued to decrease, reaching $109.53 \pm 50.16 \times 10^4/\mu L$ at week 8 (PPS population) (Fig. 2). The largest decrease in the mean platelet count in comparison with the previous week was observed at week 5, which was when the daily anagrelide dosage was increased from 0.5 to 1.0 mg/day.

During the maintenance dose evaluation period (weeks 9–52), up-titration of anagrelide further reduced the platelet counts. By week 52, the platelet count had reached $61.86 \pm 23.68 \times 10^4/\mu L$ (FAS population), which was close to the target platelet count. Nine of the 12 patients (75.0 %) achieved the target platelet count during the course of the 52-week treatment period. The median day on which the target platelet count was achieved was day 73. On the day preceding the target platelet count being reached, the mean anagrelide dose was 2.06 ± 1.31 mg/day.

During the continuation period (weeks 56–104), the mean platelet count further decreased from $63.19 \pm 25.97 \times 10^4/\mu L$ to $44.20 \pm 8.25 \times 10^4/\mu L$ (FAS population) (Fig. 3). The mean anagrelide dose during this period was 2.26 mg/day. One patient, having received a maximum dose of 5.5 mg/day, did not reach the target platelet count at any time during the entire treatment period (weeks 1–104). This dose was considered to be the maximum tolerable dose of anagrelide for this patient.

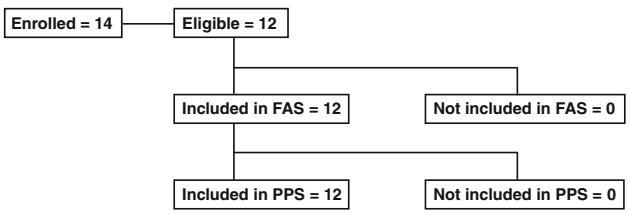

Fig. 1 Disposition of subjects in the efficacy analysis population. *FAS* full analysis set, *PPS* per protocol set

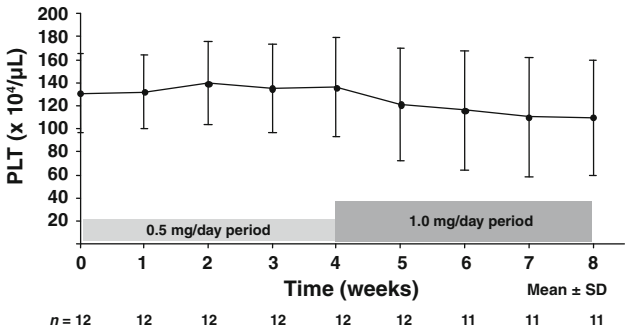

Fig. 2 Profile of platelet counts in initial dose evaluation period (PPS population). *PPS* per protocol set, *PLT* platelet count

Safety

The duration of anagrelide treatment in all patients was in the range of 756–939 days. Three patients received a dose of anagrelide exceeding 4.0 mg/day; the maximum dose administered was 5.5 mg/day.

The most commonly occurring AEs among all 12 patients are listed in Table 1. Eleven patients (91.7 %) experienced a total of 141 AEs for which a causal relationship could not be ruled out; the most common of these were palpitations, headache, diarrhea, chest pain and anemia. Five patients (41.7 %) suffered 14 AEs related to thrombosis and/or hemorrhage, of which a causal relationship could not be ruled out for 11 of these events. Three patients (25.0 %) experienced epistaxis (five AEs), two patients (16.7 %) suffered from subcutaneous hemorrhage (five AEs) and purpura (three AEs), and there was an incident of subcutaneous hematoma in one patient (8.3 %).

AEs were graded as mild (minor, requiring no special treatment or intervention, and anagrelide therapy was continued), moderate (treatment required but anagrelide therapy was continued) or severe (treatment required and anagrelide therapy was discontinued). No severe AEs occurred, with all events being mild or moderate. Six patients (50.0 %) suffered a total of 11 other AEs requiring dose reduction, and a causal relationship could not be ruled out for any of these.

One patient (8.3 %) had one other SAE, chest discomfort, for which a causal relationship could not be ruled out. This event resolved on the day of occurrence, and although this SAE was attributed to angina pectoris as a co-existing illness, the investigators were unable to rule out the possibility that administration of anagrelide may have exacerbated the event.

One other patient (8.3 %) did not achieve the target platelet count. This patient experienced headache and elevated liver enzyme parameters of alanine aminotransferase (ALT), alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γ-GTP). Although these AEs were mild or

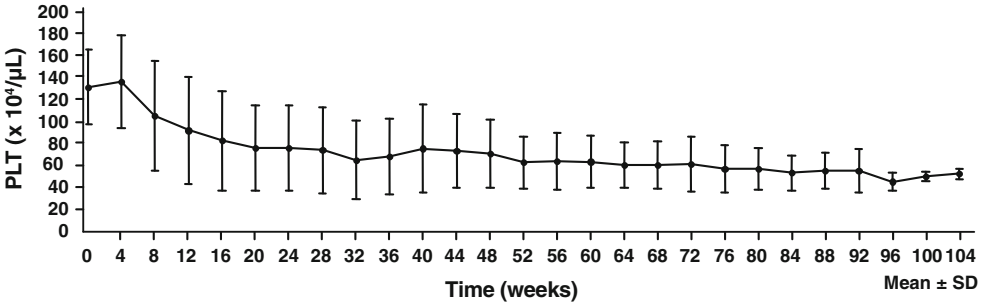

Fig. 3 Profile of platelet counts (weeks 0–104) (FAS population). *FAS* full analysis set, *PLT* platelet count

Table 1 Most common adverse events (≥5 occurrences) during entire study period, irrespective of causality

	$n = 12$	
	Number of patients (%)	Occurrences
Total number of affected patients and number of occurrences	12 (100.0)	197
Headache	7 (58.3)	20
Palpitations	6 (50.0)	20
Nasopharyngitis	7 (58.3)	14
Diarrhea	4 (33.3)	10
Chest pain	6 (50.0)	9
Anemia	5 (41.7)	5
Malaise	4 (33.3)	5
Edema peripheral	3 (25.0)	5
Upper respiratory tract inflammation	4 (33.3)	5
Epistaxis	3 (25.0)	5

moderate in nature and all resolved during the study period, a causal relationship could not be ruled out.

There were no deaths during the study. It was also noted that, from weeks 53 to 104, AEs did not increase significantly in incidence, and no unexpected or newly occurring AEs associated with anagrelide treatment were observed.

Pharmacokinetic results

Trough plasma anagrelide concentrations over the 52-week treatment period were near the lower limit of quantification (0.0929 ng/mL) in the majority of patients. Trough plasma concentrations of the active metabolite BCH24426 appeared to have reached a steady state, showing no significant variation among patients receiving the same dose of anagrelide. However, a marked variation between trough plasma concentrations of the inactive metabolite RL603 and anagrelide dose was observed in several patients.

The decision to conduct compartmental analysis was taken following completion of the study, to assist in the detailed interpretation of the PK data. The plasma concentrations of anagrelide and its metabolites were well

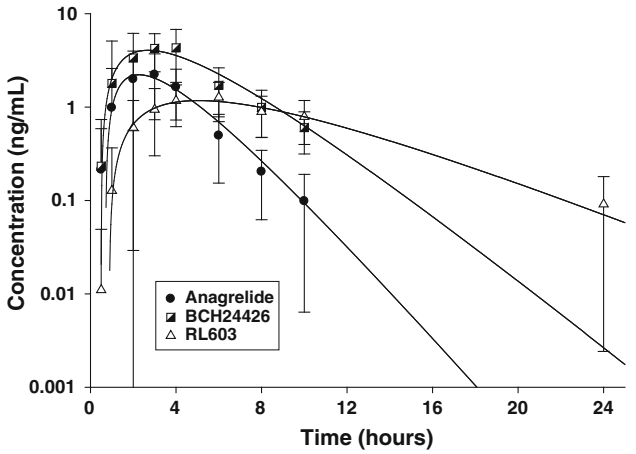

Fig. 4 Mean ± SD plasma concentrations following administration of 0.5 mg of anagrelide on day 1 (log scale)

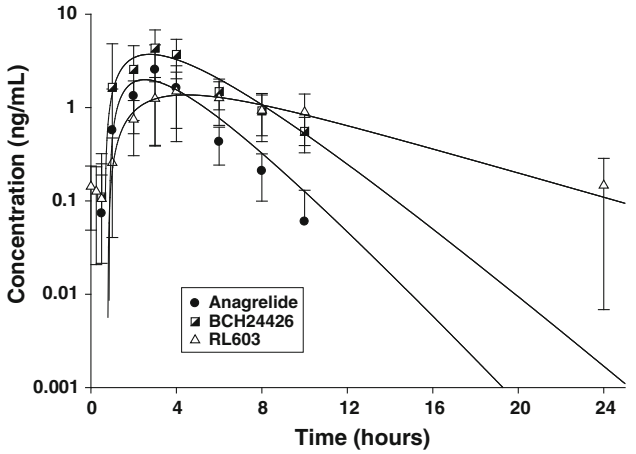

Fig. 5 Mean ± SD plasma concentrations following administration of 0.5 mg of anagrelide on day 7 (log scale)

described by the one-compartment PK model; concentration profiles were similar at day 1 and day 7 of treatment (Figs. 4, 5). PK parameters were also similar over the same intervals. Overall, the PK profile did not change over weeks 1–4 when the anagrelide dose was 0.5 mg/day (Table 2).

Following oral administration of anagrelide, there was an initial lag time of 1–1.5 h before anagrelide plasma concentrations became measureable, and a similar lag time was observed for BCH24426 and RL603. After the absorption lag time elapsed, anagrelide was absorbed rapidly [the mean absorption rate constant (k_a) ranging from 1.93 to 1.97 L/h], attaining maximum plasma concentration (C_{max}) around 2.5 h after administration. The mean time for C_{max} (t_{max}) for BCH24426 (2.75–2.81 h) and RL603 (4.20–4.35 h) occurred slightly later than the mean t_{max} for anagrelide (2.33–2.60 h). Anagrelide was eliminated rapidly with a mean terminal-phase disposition half-life ($t_{1/2}$) of 1.03–1.15 h, whereas the mean $t_{1/2}$ for BCH24426 and RL603 ranged from 1.36 to 1.45 and 4.48 to 4.55 h, respectively.

Discussion

Japanese patients naïve to any previous cytoreductive therapy were enrolled on to this study and received anagrelide as their treatment for ET. Mean platelet counts and changes in platelet count did not show a significant reduction at 0.5 mg/day (weeks 1–4). However, when dosage was increased to 1.0 mg/day (weeks 5–8), mean platelet counts decreased and changes in platelet counts decreased over time. Thus, it was concluded that 1.0 mg/day was a suitable initial dose of anagrelide to achieve a platelet-count reducing effect in this patient group.

During the first year of treatment, the target platelet count ($<60 \times 10^4/\mu L$) was achieved in nine of the 12 patients, and patients who did not meet the target platelet count still achieved a decrease from baseline. Eleven patients achieved the target platelet count at some stage before study completion; however, one patient did not reach the target platelet count at any stage during the treatment period despite being treated with a maximum tolerated dose. Over the continuation period (weeks 53–104), platelet counts were maintained, in general, at the target platelet count through up- and down-titration of anagrelide, as required. No severe AEs occurred throughout the course of the study, and no AEs led to treatment discontinuation. These findings confirm dose titration of anagrelide was well tolerated and effective in all patients in the range of 0.5–5.5 mg/day, the dose range in which platelet counts decreased in all 12 patients. Similarly, long-term maintenance treatment with anagrelide presented a sustained platelet count-reducing effect with no added safety concerns.

Although the investigators allowed for a maximum anagrelide dose of 6.0 mg/day during the dose evaluation period and 10 mg/day during the continuation period, the one patient who did not reach the target platelet count was administered a maximum anagrelide dose of 5.5 mg/day. This patient had already experienced AEs including headache and elevated liver enzyme parameters at lower doses, which were further exacerbated at a dose of 5.5 mg/day. In accordance with study protocol, this required dose reduction, initially to 5.0 mg/day, and then to 4.5 mg/day. The investigators continued to adjust the dose of anagrelide for this patient in order to achieve an acceptable level of tolerance. Thus, dose escalation beyond 5.5 mg/day was not conducted, which may explain why the patient did not achieve the target platelet count.

The most commonly observed AEs during the course of this study were headaches and palpitations (20 occurrences each), irrespective of causality. In myeloproliferative disorders such as ET, headaches are frequently reported as neurological complaints [11–13]. In addition, headache is well documented as the most common side effect associated with anagrelide treatment [14–16], although results from clinical studies have noted the incidence of headache reduces during the course of continued anagrelide therapy [14, 16, 17]. In the present study, a similar trend was

Table 2 Pharmacokinetic parameters of anagrelide and its metabolites (BCH24426 and RL603)

Analyte	C_{max} (ng/mL)	t_{max} (h)	AUC (ng h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
Pharmacokinetic model parameters for day 1					
Anagrelide	3.26 ± 2.37 [2.68]	2.33 ± 0.93 [2.16]	9.58 ± 4.87 [8.57]	1.03 ± 0.18 [1.01]	64.7 ± 29.0 [58.4]
BCH24426	5.44 ± 2.50 [4.96]	2.75 ± 1.03 [2.56]	23.0 ± 10.3 [21.3]	1.36 ± 0.54 [1.25]	25.3 ± 9.7 [23.5]
RL603	1.39 ± 0.61 [1.26]	4.35 ± 1.78 [3.99]	14.3 ± 5.4 [13.2]	4.48 ± 1.65 [4.17]	40.6 ± 16.4 [37.7]
Pharmacokinetic model parameters for day 7					
Anagrelide	2.94 ± 2.29 [2.26]	2.60 ± 0.96 [2.42]	8.15 ± 3.24 [7.53]	1.15 ± 0.44 [1.09]	72.7 ± 34.0 [66.4]
BCH24426	5.42 ± 3.10 [4.70]	2.81 ± 1.09 [2.60]	20.1 ± 6.6 [19.2]	1.45 ± 0.30 [1.42]	27.3 ± 8.7 [26.1]
RL603	1.54 ± 0.78 [1.39]	4.20 ± 1.75 [3.87]	16.1 ± 7.1 [14.8]	4.55 ± 0.64 [4.51]	36.7 ± 15.0 [33.9]

Values are mean ± SD and [geometric mean]

C_{max} maximum plasma concentration, t_{max} mean time for C_{max}, *AUC* area under plasma concentration–time curve, $t_{1/2}$ mean terminal-phase disposition half-life, *CL/F* oral-dose clearance

observed over time: up to week 52, seven patients (58.3 %) reported headache, falling to four patients (33.3 %) by week 104. From week 105 onwards, this further reduced to one patient (8.3 %).

Similarly, palpitations are also recognized as one of the most common treatment-related AEs associated with anagrelide therapy [18]. As is the case with most observed side effects, this may be attributed to the direct vasodilating and positive inotropic effects of anagrelide [19]. Thus, it can be concluded that the safety profile of anagrelide in this study was consistent with that observed in other clinical studies with anagrelide.

It should be noted that the exclusion criteria for this study were highly restrictive, thus only patients in generally good health were enrolled. In particular, patients with a history of thrombohemorrhagic events were excluded. By nature, early phase I/II studies are small in patient numbers, and both these factors place limitations on the results from this study being representative of the Japanese population as a whole. Patients enrolled onto this study were receiving the investigational product as their first-line treatment for ET, which may mean that these patients were at an early stage in their disease progression. Thus, intervention at this point would arguably have more significant benefit. Moreover, measures to avoid tolerability issues included a low initial dose of anagrelide, gradual incremental dose increases in accordance with the pre-defined product dose adjustment, coupled with careful monitoring of patients. Taken together, these considerations may explain why only one SAE occurred during the course of the study.

The rationale for administering anagrelide at an initial dose of 0.5 mg/day was due to the low average weight of the Japanese population (60 kg). In contrast, the average weight of other non-Japanese adults is widely accepted as 70 kg. Thus, in order to normalize for body weight, the initial dose was set low because it was considered that a dose of 0.5 mg/day may have produced a sufficient platelet lowering effect in Japanese patients and be readily tolerated.

Previous PK studies have suggested that anagrelide is well absorbed (bioavailability $\geq$75 % based on total radioactivity recovery in urine following administration of ^{14}C-anagrelide 1 mg) and is rapidly and extensively metabolized via CYP1A2 in the human body to form the active metabolite BCH24426 [20, 21]. In addition, less than 1 % of an administered dose is recovered in urine as unchanged anagrelide [20]. BCH24426 is subsequently eliminated in roughly equal amounts by renal clearance and by metabolism to the inactive metabolite, RL603. Although the PK profile of anagrelide is not affected by renal impairment, the clearance of BCH24426 is reduced and its $t_{1/2}$ prolonged in subjects with severe renal impairment.

The PK data from this study were found to be in line with a previous PK study in healthy Japanese volunteers (T. Tanaka, M. Ohtsuji, R. Urae; AGR-I-01-J Clinical Study Report, 2000). However, the Japanese patients with ET in this study had slightly higher C_{max} and area under plasma concentration–time curve (AUC) values for both anagrelide and BCH24426 compared with adult non-Japanese patients with ET [10] (Table 3). Myrand et al. [22] recently reported that Caucasians exhibit approximately 29 % (95 % confidence interval 19 %, 40 %) more CYP1A2 activity than native Japanese populations. The higher anagrelide plasma concentrations in Japanese patients with ET in this study may reflect the high inter-subject PK variability, which is common in compounds exhibiting extensive pre-systemic metabolism, as well as modest differences in CYP1A2 activity between native Japanese and non-Japanese populations.

Yasuda et al. [9] suggested that differences in ethnicity may lead to variation in the PK of a drug. Differences in drug-metabolizing enzymes, transporters and pharmacodynamic (PD) targets between ethnic groups are potential contributing factors to observed differences in drug responses between populations. These observed differences include toxicity profiles of drugs, the absence or presence of genes implicated in metabolic pathways, and trough concentrations of drugs. Similarly, diet and concurrent medication regimes may also be of relevance [9].

Previous attempts to examine the PK/PD relationship between the change in platelet counts and the exposure to anagrelide and BCH24426 have shown a general trend that only explains a small part of the variability in the platelet count response to anagrelide treatment [23]. This relationship could be explored better using a physiologically based PK/PD modeling approach that simultaneously evaluates the effects on platelet count, thrombopoietin (TPO), and megakaryocytes [24, 25]. In such models, the number of megakaryocytes can be estimated from the literature, but it is important to measure changes in platelet counts and changes in TPO levels simultaneously. Since TPO levels were not measured in this study, the ability to more robustly evaluate this PK/PD relationship was limited.

Cacciola and colleagues [26] reported findings from an additional study of 17 non-Japanese patients with ET, where the anagrelide dose was started at 0.5 mg/day and titrated in increments of 0.5 mg/day every week until the target platelet count ($<50 \times 10^4/\mu L$) was reached. The average maintenance dose of anagrelide in their study (2.1 mg/day, range 0.5–6.0 mg/day) was very similar to the average anagrelide dose in our study on the day before the target platelet count was reached (mean anagrelide dose, 2.06 $\pm$ 1.31 mg/day). Thus, these similarities, in addition to the aforementioned modest differences in PK exposures between Japanese and non-Japanese patients with ET (Table 3), may indicate that different dosing regimens are

Table 3 Steady-state pharmacokinetic parameters in Japanese and non-Japanese patients with essential thrombocythemia receiving anagrelide: C_{max} and AUC normalized to 1 mg dose

Analyte/population	C_{max} (ng/mL)	t_{max} (h)	AUC (ng h/mL)	$t_{1/2}$ (h)
Anagrelide				
Japanese ($n = 12$)	5.88 ± 4.58	2.33 ± 0.93	16.3 ± 6.5	1.15 ± 0.44
Non-Japanese				
Adult (18–50 years) ($n = 12$)	2.81 ± 0.99	1.17 ± 0.39	6.8 ± 2.4	1.32 ± 0.39
Elderly (≥65 years) ($n = 12$)	3.97 ± 1.44	1.33 ± 0.91	11.2 ± 4.0	1.41 ± 0.27
BCH24426				
Japanese ($n = 12$)	10.84 ± 6.20	2.75 ± 1.03	40.2 ± 13.2	1.45 ± 0.30
Non-Japanese				
Adult (18–50 years) ($n = 12$)	8.02 ± 3.74	0.96 ± 0.26	29.6 ± 10.9	2.70 ± 0.52
Elderly (≥65 years) ($n = 12$)	5.02 ± 3.47	1.29 ± 0.99	20.5 ± 14.8	3.64 ± 1.08
RL-603				
Japanese ($n = 12$)	3.08 ± 1.56	4.35 ± 1.78	32.2 ± 14.2	4.55 ± 0.64
Non-Japanese	NC	NC	NC	NC

Values are mean ± SD

C_{max} maximum plasma concentration, t_{max} mean time for C_{max}, *AUC* area under plasma concentration–time curve, $t_{1/2}$ mean terminal-phase disposition half-life, *NC* not calculated

not needed for these two populations. The dose of anagrelide required to lower platelet counts to within the target range in Japanese patients with ET, will be further evaluated in the ongoing phase III study in Japan (SPD422-308, NCT01214915 [27]).

In addition, during our study, treatment with anagrelide was carefully titrated to a patient-specific optimal dosing regimen based on individual response of platelet count and tolerability. This individualized and carefully managed titration can accommodate PK differences as well as PD differences among this group of patients.

In conclusion, the efficacy and selectivity of anagrelide in reducing and maintaining platelet count levels in non-Japanese patients with ET have been previously demonstrated. Our study findings have indicated that the metabolism of anagrelide is modestly lower in Japanese patients than in non-Japanese patients, but that these differences did not translate to different clinical outcomes. Furthermore, this study confirms that anagrelide is efficacious and well tolerated in this small cohort of Japanese patients with ET.

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