A phase III randomized, multicentre, double blind, active controlled trial to compare the efficacy and safety of two different anagrelide formulations in patients with essential thrombocythaemia – the TEAM-ET 2.0 trial

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Summary

Anagrelide is an established treatment option for essential thrombocythaemia (ET). A prolonged release formulation was developed with the aim of reducing dosing frequency and improving tolerability, without diminishing efficacy. This multicentre, randomized, double blind, active-controlled, non-inferiority trial investigated the efficacy, safety and tolerability of anagrelide prolonged release (A-PR) over a reference product in high-risk ET patients, either anagrelide-naive or -experienced. In a 6 to 12-week titration period the individual dose for the consecutive 4-week maintenance period was identified. The primary endpoint was the mean platelet count during the maintenance period (3 consecutive measurements, day 0, 14, 28). Of 112 included patients 106 were randomized. The mean screening platelet counts were 822 × 10^9/l (95% confidence interval (CI) 707–936 × 10^9/l) and 797 × 10^9/l (95% CI 708–883 × 10^9/l) for A-PR and the reference product, respectively. Both treatments effectively reduced platelet counts, to mean 281 × 10^9/l for A-PR (95% CI 254–311) and 305 × 10^9/l (95% CI 276–337) for the reference product (P < 0.0001, for non-inferiority). Safety and tolerability were comparable between both drugs. The novel prolonged-release formulation was equally effective and well tolerated compared to the reference product. A-PR provides a more convenient dosing schedule and will offer an alternative to licensed immediate-release anagrelide formulations.

Keywords: anagrelide, essential thrombocythaemia, pharmacodynamics, pharmacokinetics, safety.
Essential thrombocythaemia (ET) is a myeloproliferative neoplasm characterized by a sustained elevation in platelet counts (>450 x 10^9/l) caused by increased megakaryopoiesis in the bone marrow (Barbui et al, 2015). ET is associated with an increased risk of thrombosis and/or haemorrhage, as well as progression to myelofibrosis (Passamonti et al, 2008; Barbui, 2011). The most important risk factors include previous thromboembolic events, age >60 years, and JAK2 V617F mutation (Barbui et al, 2011; Prajs & Kuliczkowski, 2017).

Cytoreductive therapy is recommended for these patients (Barbui et al, 2011).

Anagrelide, an established treatment option for ET (Kanakura et al, 2014; Kreher et al, 2014; Samuelson et al, 2015), was originally developed as an inhibitor of platelet aggregation because, together with its active metabolite 3-hydroxyanagrelide, it inhibits the cyclic AMP phosphodiesterase III within platelets (Fleming & Buyniski, 1979; Ahluwalia et al, 2015; Espasandin et al, 2015). However, even low doses of the drug exert profound thrombocytopenic actions (Silverstein et al, 1988). It was recently demonstrated that anagrelide inhibits the maturation of megakaryocytes and thereby reduces platelet counts (Abe Andes et al, 1984; Ahluwalia et al, 2015). Moreover, anagrelide seems to be more effective in reducing venous thrombosis compared to the second most widely used ET treatment, hydroxyurea (also known as hydroxyurea) (Samuelson et al, 2015). In contrast to hydroxyurea, anagrelide is thrombocyte-specific and therefore does not suppress other cell lineages (Fruchtman et al, 2005). Finally, anagrelide treatment may be associated with a lower leukaemogenic risk compared to other treatments (Fruchtman et al, 2005).

The most common side effects of anagrelide include palpitations, tachycardia, headache, dizziness and anaemia (Fruchtman et al, 2005; Petrides, 2006). The occurrence of such side-effects may be associated with high doses, high plasma concentrations of anagrelide or its active metabolites, whereas the platelet-reducing effects of anagrelide do not depend on high plasma concentrations (Petrides, 2006; Petrides et al, 2009). Therefore a prolonged release formulation of anagrelide (A-PR) was developed (Petrides et al, 2018). In a phase I trial, the relative bioavailability compared to a reference product (RP) was 55% under fasting conditions and 60% under fed conditions (Petrides et al, 2018). As expected for a prolonged release formulation, the maximum concentration (Cmax) and the area under the curve (AUC) were lower, while the time at which the Cmax is observed (Tmax) and the terminal elimination half-life were longer compared to the reference product (RP) (Petrides et al, 2018). The current randomized, double blind, multicentre, multinational trial aimed to compare the efficacy, safety and tolerability of A-PR and the RP in anagrelide-naïve and –experienced ET patients with an indication for cytoreductive treatment. In a titration period of 6–12 weeks, the individual dose was identified, and the efficacy criteria were assessed over a 4-week maintenance period.

We hypothesized, that an extended release formulation of anagrelide may be equally efficacious in lowering platelet counts compared to the licensed RP, with potential benefits regarding dosing frequency and tolerability.

**Methods**

**Study design**

This trial was a randomized, multicentre, double blind, active controlled trial to investigate the efficacy, safety, tolerability and pharmacokinetics of two anagrelide formulations, the test product, a prolonged-release formulation (A-PR, AOP Orphan Pharmaceuticals AG, Vienna, Austria) and the licensed RP, an immediate release formulation (Thromboreductin, AOP Orphan Pharmaceuticals AG, Vienna, Austria). The trial was conducted between March 2014 and April 2015 in 18 centres in Austria (3), Bulgaria (2), Lithuania (2), Poland (5) and Russia (6). A favourable opinion of the relevant independent ethics committees and the competent authorities was obtained prior to the start of the trial. The trial complied with the ethical principles set forth in the Declaration of Helsinki and the Good Clinical Practice guideline.
by the International Conference for Harmonisation. The trial was registered at the EudraCT database with the identifier 2013-003410-41 (http://www.clinicaltrialsregister.eu/ctr-search). All patients gave their oral and written informed consent prior to entry into the trial. The study design followed the recommendations of the European Medicines Agency “Note for Guidance on modified release oral and transdermal dosage forms, Section II” (CPMP, 1999) and “Points to consider on the clinical requirements of modified release products submitted as a line extension of an existing marketing authorization” (CPMP 2002, 2003). The full protocol is available from the corresponding author upon request.

Detailed inclusion and exclusion criteria are listed in the Table SI. Briefly, patients diagnosed with ET according to the 2008 World Health Organization criteria (Tefferi & Vardiman, 2008) and at a high risk, with or without prior treatment, were available for inclusion.

Patients were randomized to receive an A-PR or RP in a 1:1 ratio. Participants were allocated to unique identification numbers in sequential order according to their admission to the study. Randomization was performed using an interactive web response system that assigned a kit number to one of the two treatments. The randomization was stratified based on previous anagrelide exposure and age (<60/≥60 years of age). After randomization, patients entered a titration period, which lasted 6–12 weeks. As soon as two consecutive platelet counts were “stable” (definition of “stable” see supplementary information) patients entered the maintenance period, which lasted for 4 weeks. The end of study and safety follow-up visit was 28 days after the end of the maintenance period. An overview of the trial design is presented in Fig 1. An independent safety data monitoring committee was established as an additional safety measure. Both patients and treating physicians were blinded.

**Study drug and dosing**

The initial dose for anagrelide-naïve patients was 1 mg of the RP or 2 mg A-PR. Based on the relative bioavailability of 55% of A-PR compared to the RP these doses were assumed to be equivalent (Petrides et al, 2018). Ten dose levels were defined, ranging from 0.5 to 5 mg for the RP and from 1 to 10 mg for the A-PR (Fig 2). Anagrelide pre-treated patients were switched within the respective dose level. Dosing was adjusted weekly, if required, according to the platelet response (target: 150–400 × 10^9/l). Weekly titration was done in 0.5 mg steps in the reference group and in 1 mg steps in the A-PR group. The maximum daily doses were 5 mg for the RP and 10 mg for A-PR. In general, the RP is dosed twice daily, while A-PR may be dosed once or twice daily, depending on the dose level. To maintain the double-blind character of the trial in some dosing levels the use of placebo capsules was necessary. All pills were encapsulated and provided in blister packs. Each patient received a plan, explaining which pill of the blister pack had to be taken in the morning or in the evening. If possible, the morning and evening dose were equally split. However, for odd dose levels, daily doses did not alternate between the last day of 1 week and the first day of the following week, which may impact pharmacokinetic analysis.

**Analyses**

Platelet counts for the primary efficacy analysis were performed in a central laboratory. Samples were transferred to the central laboratory in validated ambient transport boxes, which offered stability for platelets for a minimum of 120 h. Dose titration and safety platelet counts were also performed in local laboratories.

Furthermore, in all patients drug concentrations were measured by liquid tandem mass spectrometry during the maintenance phase at Day 0, 14 and 28 prior to the next planned intake of the trial drugs, while in some patients, who had taken a stable dose of the trial drugs ≥5 days and who specifically agreed to participate in this part of the trial, a concise pharmacokinetic analysis was performed with blood samples drawn at predefined time-points (~1 min, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 13, 14, 15, 16, 18, 20 and 24 h after the morning dose) on Day 7 of the maintenance period.

Safety parameters were analysed in the local laboratories. Quality of Life (QoL) was assessed using EQ-5D-3L questionnaire (EuroQol Group 1990).

**Endpoints**

This trial was designed to show of A-PR compared to RP the primary endpoint: platelet counts were assessed at three time points during the maintenance period (Days 0, 14 and 28).

Secondary endpoints comprised platelet response status, tolerability and safety of the trial drugs. The platelet response status was defined as: (i) a mean platelet level <600 × 10^9/l, (ii) an increase in the platelet count of ≤300 × 10^9/l during the maintenance therapy, (iii) no platelet count >1000 × 10^9/l or (iv) a platelet count between 150 and 400 × 10^9/l during the whole maintenance phase. The time from randomization until the maintenance phase and the time to withdrawal of the trial drugs was analysed.

Drug concentrations were analysed at the respective time points. In an additional analysis we compared the number of patients with platelet counts below or above the predefined upper limit of the reference range (370 × 10^9/l).

Safety and tolerability assessment included laboratory values (blood cell counts, chemistry, coagulation, urinalysis), physical examination, vital signs, electrocardiogram (ECG) evaluation, echocardiography, QoL assessment and N-terminal pro-brain natriuretic peptide. Adverse event (AE) were documented throughout the trial.
Statistical analysis

Efficacy analysis. The primary efficacy endpoint (mean platelet counts during the maintenance period) was analysed by means of a repeated measurement analysis using a mixed model, which included treatment, time, stratification variables, age and cardiovascular medical history (yes/no). Platelet counts were log-transformed.

The two-sided 95% confidence interval (CI) for the treatment difference was computed based on the corresponding factorial mixed model for repeated measurements (MMRM, see above), which is equivalent to calculating a one sided 97.5% CI for the ratio of means. Non-inferiority of A-PR was concluded if the upper limit of the two-sided 95% CI of the treatment difference between the A-PR and the RP did not exceed 1.3 (0.262 on the ln scale). Corresponding equivalent one-sided P-values for the test decision of the hypothesis were calculated.

Response rates were calculated, tabulated, stratified by pretreatment status and treatment groups were compared using
the Fisher’s exact test and 95% (two-sided) unconditional exact CIs. Time from randomization until entrance in the maintenance phase was summarized using descriptive statistics and compared using a Cox model. Time to withdrawal was similarly analysed. The number of titrations and the maintenance dose (stratified by pretreatment status) were analysed using descriptive statistics. Absolute and relative changes from baseline in the platelet counts were analysed descriptively and also using an ANCOVA model of the original log-transformed data of absolute platelet count with the same covariates used for the analysis of the primary endpoint. Results of the QoL analysis using the EQ-5D-3L were descriptively analysed. Pharmacokinetic data, laboratory data, adverse events, ECG abnormalities, echocardiographic findings and vital signs were tabulated and analysed descriptively. Comparisons between treatments were performed using Chi-Square of Fisher’s exact test.

Sample size. The sample size was calculated to show non-inferiority between A-PR and the RP with regards to platelet counts during the maintenance period. Non-inferiority of A-PR was concluded if the upper limit of the two-sided 95% confidence interval (CI) of the treatment difference between the A-PR and the RP did not exceed 1.3 (0.262 on the ln scale), which is equivalent to calculating a one-sided 97.5% CI for the ratio of the means. The rationale for the choice of the non-inferiority margin is presented in the supplement.

The sample size calculation was based on data from a previous trial (Steurer et al, 2004) assuming a power of 80%, a significance level of 2.5% and a variance of 0.2 (standard deviation 0.4472, on the ln scale) applying a one-sided t-test for mean differences. Stratification was applied according to age and pre-treatment status and the non-inferiority criteria defined in the following. The required sample size, taking

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<th>Patient disposition and demographics</th>
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In total, 112 patients were screened: 54 were randomized to receive A-PR and 52 were randomized to receive the RP (Fig 1). There were six screening failures, of which one was already randomized explaining the discrepancy of patients in both groups. Forty-three and 48 patients completed the trial per protocol in the RP group and in the A-PR group, respectively. Reasons for discontinuations are presented in Fig 1 and Table SII. In the A-PR group, 6 patients withdrew during the titration period, none in the maintenance or the follow-up period, while in the RP group, 7 patients dropped out during the titration period, one during the maintenance phase and one during the follow-up phase. Demographic characteristics and medical history are presented in Tables I and SIII. Treatment compliance, defined as actual study drug intake was checked by returned patient diaries and returned used/unused blister packs and was 96% for A-PR and 97% for RP. The trial ended after the last randomized patient completed the trial.

Primary endpoint

The mean platelet counts in the per-protocol analysis set ranged between 308 and 322 × 10⁹/l for A-PR for the three assessed time points and between 330 and 348 for the RP. The point estimates for adjusted mean platelet counts in the maintenance period were 281 × 10⁹/l (95% CI 254–311) for A-PR (n = 52) and 305 × 10⁹/l (95% CI 276–337) (n = 54) for the RP group. The ratio of the platelet counts was 0.92 (95% CI 0.817–1.037). The upper limit of the one-sided 97.5% CI was 1.037 and the primary endpoint of this trial was met with a P < 0.0001. This demonstrated non-inferiority of A-PR. Cardiovascular medical history had no significant impact, and no significant cross effect between time and treatment was detected.

Platelet count and response rates

There was no difference between treatments regarding response rates (Table II).

In an additional analysis, we compared the number of patients with platelet counts above or within the reference range (370 × 10⁹/l) at the end of treatment, both in naïve and pre-treated patients (Table III). More patients treated with A-PR had platelet counts within the reference range of platelets, indicating more stable effects. This effect was most pronounced in treatment-naïve patients or patients pre-treated with a platelet reduction different from anagrelide.
During the trial, platelet counts decreased in most patients with prior anagrelide treatment: In six of seven pre-treated patients receiving A-PR platelet counts decreased by a mean $137 \pm 126 \times 10^9/l$ (SD). In the RP group, platelet counts dropped by a mean $111 \pm 102 \times 10^9/l$ (SD) in 6 of 7 patients. To comply with the strict requirements of the study regarding platelet counts, in the A-PR group the dose level was not changed in four patients, decreased in two patients and increased in one patient; in the RP group the dose was raised in five patients, remained unchanged in one patient and decreased in one patient during the trial. In the RP group, the dose level was raised by mean 1-4 levels, whereas overall the dose level remained unchanged in the A-PR group.

There was no difference in the time from randomization until entry to the maintenance period between patients taking A-PR (median 42 days) or the RP (median 42 days). The covariates, pre-treatment status, age or cardiovascular medical disease, had no impact.

The mean maintenance dose was 3 mg for A-PR and 2 mg for the RP. The number of patients per dose level at the beginning of the maintenance period is presented in Fig 2. In the A-PR group, about three quarters of all patients could be treated with 1 or 2 tablets per day, while in the RP group this number of tablets sufficed only in about 10% of all patients (Fig 2).

The mean time to withdrawal of the trial drugs was 109 days for A-PR and 106 days for the RP.

### Quality of life
At inclusion into the trial, the mean baseline QoL assessed by the EQ-5D-3L questionnaire was slightly lower in the A-PR group compared to the RP group (0.81 vs. 0.85).
During the titration phase, the mean score increased to 0.85 in the A-PR group and to 0.87 in the RP group and remained stable throughout the maintenance period (0.85 A-PR vs. 0.88 RP group).

Pharmacokinetics

Detailed pharmacokinetic data were obtained from 12 patients taking A-PR and 11 patients receiving the RP (Tables SIV and SV). As expected, the $C_{\text{max}}$ and the $\text{AUC/D}$ was lower, and the $T_{\text{max}}$ and the half-life were longer for A-PR compared to the RP. Interestingly, the AUC was lower in the A-PR group in the morning, but higher in the evening, with substantially less variation in the different measurements, which indicates more stable plasma concentrations. However, this was not primarily a pharmacokinetic study and, due to the dosing schedule, which led to the frequent intake of alternating doses, pharmacokinetic comparisons should be made with caution.

Safety

There was no difference in the duration of drug exposure between both groups. A total of 261 AEs were reported in the group taking A-PR, whereas 228 AEs were reported in the RP group (Fig 3). Except for gastrointestinal AEs, which occurred more frequently in the A-PR group (47 vs. 24, $P = 0.048$) the occurrence and the distribution of AEs over both treatment groups was similar. Forty cardiac AEs in 19 patients were reported in the A-PR group, while 65 cardiac AEs were documented in 26 patients in the RP group. An exact listing of adverse events is presented in Table SVI.

Palpitations ($n = 31$ in A-PR, $n = 47$ in RP) and tachycardia ($n = 6$ in A-PR, $n = 15$ in RP) were regularly judged as being an adverse drug reaction. However, there was no difference in cardiac adverse drug reactions between both groups. Also gastrointestinal disorders were frequently deemed to be connected to the intake of A-PR or the RP ($n = 29$ vs. $n = 15$, no significant difference).

![Fig 3. Adverse events divided by system organ class. The figure displays the adverse events reported throughout the trial. Gastrointestinal disorders occurred more frequently in the Anagrelide Prolonged Release group compared to the Reference Product group ($P = 0.048$). There was no significant difference in other system organ classes ($n = 52$ for anagrelide prolonged release and $n = 54$ for reference product).](image-url)
Adverse events of special interest (AESI), including headache, tachycardia, dizziness, palpitation, nausea, vomiting, diarrhoea and abdominal pain (119 A-PR vs. 123 RP group) were not different between groups. Neither were AEs related to ET (24 A-PR vs. 23 RP). Ten patients experienced 18 serious AEs in the A-PR group, of which only one was related to the study drug, an episode acute pancreatitis; and six were considered related to ET. In the reference group, one patient experienced two serious AE, not considered to be related to the study drug or ET. One patient, who received A-PR, died of pneumonia and haemorrhagic cystitis that was considered unrelated to the trial drug. A complete list is presented in Table SVII. Three subjects receiving A-PR and four subjects taking the RP withdrew from the trial due to AEs.

Changes in laboratory values are presented in the supplement.

Discussion

The results of this phase III trial demonstrate non-inferiority of A-PR to the reference immediate-release anagrelide formulation (RP) with regards to the primary efficacy criterion: the platelet counts during the maintenance period of the trial. Even in pre-treated patients, platelet counts decreased after inclusion, indicating the strict requirements of the trial and the efficacy of both trial drugs.

In each group, the trial drug was titrated based on platelet counts and tolerability. The mean doses during the maintenance period were comparable (2 mg RP, 3-5 mg A-PR), considering the relative bioavailability of A-PR (58%) compared to immediate-release anagrelide (Petrides et al, 2018). The mean dose of the RP was also similar in other clinical trials investigating the effects of other anagrelide products with a similar titration plan (Okamoto et al, 2013; Kanakura et al, 2014). However, both substances were equally effective in the predefined platelet response rates. Notably, the trial was designed to test non-inferiority of the two formulations rather than superiority. The primary endpoint of the trial, platelet counts during the maintenance period, was chosen because high platelet counts are associated with a higher risk to develop thrombosis in ET patients (Piccin et al, 2015; Buxhofer-Ausch et al, 2016; Schwarz et al, 2016).

Interestingly, for anagrelide pre-treated patients switching to A-PR led to lower platelet counts at identical dose level, or required lower doses to keep the platelet count constant. Moreover, fewer patients had platelet counts above the reference range at the end of the maintenance period and platelet counts were, overall, lower in the A-PR group. One may speculate that these results hint to a higher efficacy of A-PR compared to the RP, possibly due to more constant plasma concentrations of this formulation.

Anagrelide reduces the platelet count by inhibiting the maturation of megakaryocytes. Consequently, the decreases in platelet count are noticeable over a period of days to weeks, and after discontinuation of the drug, platelet counts return to pre-therapeutic values within only 4–7 days (Petrides et al, 2009; Gisslinger et al, 2013). On the other hand, the most prominent side effects of anagrelide are pathophysio logically linked to inhibition of phosphodiesterase III, which requires higher plasma concentrations than its effects on megakaryocytes in the bone marrow (Espasandin et al, 2015). Therefore, the platelet inhibitory actions of anagrelide may be separable from its side effects. Thus, the use of a prolonged-release formulation of anagrelide may improve tolerability without reducing its efficacy. This hypothesis was supported by the results of a previous trial comparing two distinct anagrelide formulations. In this small trial, the number of AEs was lower in the group with lower peak plasma concentrations (Petrides et al, 2009). In general, the observed AEs are similar to the AEs observed in other clinical trials (Petrides et al, 2009; Okamoto et al, 2013; Kanakura et al, 2014). However, there was no numerical reduction in AEs in patients treated with A-PR, but a different profile of AEs was observed between the two groups. The prolonged release formulation seemed to cause more AEs in the gastrointestinal system. On the other hand, there was a numerical reduction in cardiac adverse events, which are of special interest in anagrelide-treated patients and may lead to discontinuation of treatment (Tortorella et al, 2015). The number of SAEs was numerically higher in the A-PR group compared to the RP group. However, only one SAE was deemed related to the study drug (an episode of acute pancreatitis). Whether this observation was due to chance or not needs to be clarified in future trials.

For the RP, 0.5 mg tablets were available and morning and evening dose differed by maximum 0.5 mg to achieve odd dosing levels. On the other hand, only 2 mg tablets were available for A-PR. Thus, the dosing schedule differed relevantly in the two trial groups. The lowest possible dose was 2 mg for A-PR every other day. However, this dose is 4-fold higher compared to the lowest dose for the RP or, taking the relative bioavailability into account, more than 2-fold higher regarding plasma concentrations. This may, at least partly, account for some AEs in the A-PR group, especially at lower doses. Moreover, it has already been demonstrated that the used RP may have improved tolerability in comparison to other marketed substances, which could make further improvements difficult to detect (Petrides et al, 2009).

The use of extended release formulations may offer an important advantage by reducing the dosing frequency and the total number of pills patients have to take. A higher pill burden was associated with poor therapy adherence and worse clinical outcomes in various chronic diseases (Coleman et al, 2012; Nachega et al, 2014; Xie et al, 2014; Leslie et al, 2018). Interestingly, an economic model calculated the costs of switching renal transplant patients from a regimen with two daily tacrolimus doses to single daily dose treatment. The improvement of therapy adherence and the consequential reduction of clinical events and hospitalizations led to substantial cost reductions over a period of 5 years.
Ahluwalia, M., Butcher, L., Donovan, H., Killick-Tmax was longer, compared to the RP. Notably, the pharmacokinetic parameters found in another trial involving patients morning and evening, are comparable to the pharmacokinetic parameters of dose level 4 of the RP, which represent an intake of 2 tablets for the reference group in the morning and evening, are comparable to the pharmacokinetic parameters found in another trial involving patients with ET, which indicates external validity (Okamoto et al, 2013). The AUC per administered dose was much higher for the RP, indicating the lower relative bioavailability of A-PR compared to the RP. These results confirm that intake of A-PR generates more stable plasma concentrations. Additionally, for patients experiencing AEs, which may be associated with high plasma concentrations of anagrelide or its metabolites, the use of a prolonged release formulation may alleviate such AEs and improve tolerability.

Limitations: This trial was designed to demonstrate non-inferiority with regard to platelet control and safety of A-PR. Due to the short exposure of only 4 weeks after the titration period, the expected advantages in tolerability of the novel A-PR could not be assessed in this trial. Moreover, this trial was not powered to compare safety or tolerability between both groups. Furthermore, dosing schedule and the double-blind character of the trial made pharmacokinetic analysis difficult. Comparisons between dose levels are presented in Table SIV, but are also affected from alternating doses on the previous trial days. However, it is also important to mention that these measurements were not the main focus of this trial.

In conclusion, the findings of this trial demonstrate non-inferiority between A-PR and immediate release anagrelide. Safety and tolerability were comparable between both trial products. The use of A-PR provides an option for a more convenient dosing schedules. Patients with AEs associated with high plasma concentrations of anagrelide may benefit from the use of A-PR.

Conflicts of Interest
JH and CK are employees of AOP. HG, VBA, and SB received honoraria and consulted AOP.

Sources of Funding
AOP Orphan Pharmaceuticals funded the trial. JH and CK work at AOP Orphan Pharmaceuticals.

Author Contributions
HG, JH and CK designed the trial. All authors were involved in patient recruitment and the conduct of the trial. HG, JH, CK, CS and BJ analyzed and interpreted the data. CS, BJ and CK drafted the manuscript. All authors critically revised and approved the manuscript.

Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Inclusion and exclusion criteria.
Table SII. Discontinuation of the trial.
Table SIII. Medical history according to system organ classes.
Table SIV. Pharmacokinetic parameters on Day 7 – independent of dose levels.
Table SV. Pharmacokinetics by dose levels (dose level 2 to 4).
Table SVI. Adverse events.
Table SVII. Serious adverse events.

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