482 *PTG-300 Eliminates the Need for Therapeutic Phlebotomy in Both Low and High-Risk Polycythemia Vera Patients*

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Background

Polycythemia vera (PV) patients are treated with periodic therapeutic phlebotomy (TP) in order to maintain hematocrit levels <45% in an effort to reduce the incidence of thrombotic events [Marchioli NEJM 2013]. Since, they are seen periodically, PV patients likely spend significant time with hematocrit levels >45%, thereby potentially increasing their risk of thrombosis. Symptomatic iron deficiency represents a challenge in PV as it is commonly present at diagnosis [Ginzburg Leukemia 2018] and worsens after repeated and/or frequent TP, and often symptomatic from their iron deficiency. We hypothesized that both iron deficiency and expanded erythropoiesis in PV lead to suppression of hepcidin, the body's main negative regulator of iron metabolism, and that hepcidin suppression enhances iron absorption and availability for enhanced erythropoiesis in TP-requiring PV patients.

We previously demonstrated that PTG-300, a hepcidin-mimetic, caused dose-related anemia in preclinical studies. In a phase 2 trial in β-thalassemia, PTG-300 leads to a sustained (3-7 days) decrease in serum iron and transferrin saturation (TSAT) but did not demonstrate off-target effects. The current study aims to compare the iron status and phlebotomy requirements in high TP-requiring PV patients before and during treatment with PTG-300 (Figure 1).

Methods

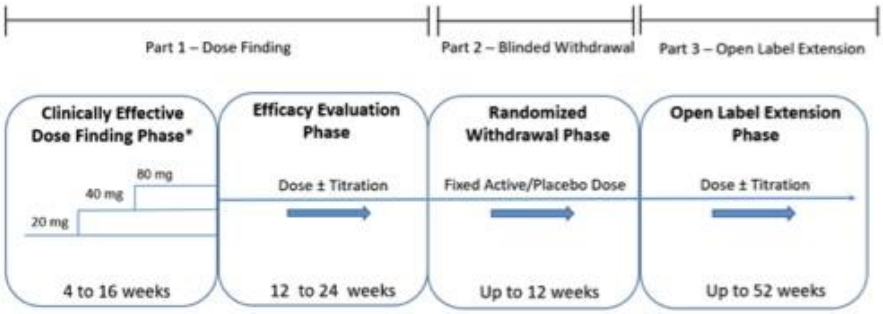
PTG-300-04 is a 3-part Phase 2 trial consisting of (1) a 28-week dose-finding; (2) a 12-week blinded randomized withdrawal (1:1) PTG-300 vs placebo; and (3) a 52-week open label extension (**Figure 1**). Eligibility criteria include PV diagnosis (by 2016 WHO criteria) and ≥3 phlebotomies with or without concurrent cytoreductive therapy to maintain hematocrit ≤45% in the 24 weeks prior to enrollment. PTG-300 doses of 10, 20, 40, 60 and 80 mg administered subcutaneously weekly were adjusted to maintain hematocrit <45%.

Results

Thirteen subjects were enrolled to date: 7/13 with low risk, mean age 57.4 years (range 31-74). Six receiving TP alone, 6 concurrent hydroxyurea, 1 on concurrent interferon; TP in the 24 weeks prior to enrollment = 3-9; median time between TP = 42 days. After instruction, each of the patients self-administered the drug at home. Eight subjects have been treated for ≥3 months with PTG-300 (**Figure 2a**). Three subjects have been randomized. During the open label dose finding portion of the study, all subjects were phlebotomy-free with the exception of one subject. Three subjects completed part 1 (28 weeks) with no TP as compared to 3-5 TP required in a similar period prior to study initiation. During the 28-week dose-finding period, the hematocrit was continuously controlled below 45% in all but two subjects' (**Figure 2b**). Two subjects had hematocrits transiently >45% but remained below 45% after phlebotomy in one and dose increase in both. Furthermore, erythrocyte numbers decreased (**Figure 2c**) and MCV increased in all but two subjects. These findings suggest a redistribution of iron within erythropoiesis. Lastly, prior to treatment, mean iron-related parameters were consistent with systemic iron deficiency while serum ferritin increased progressively toward normal range**.** Most frequent adverse events were injection site reaction (ISR) reported by three patients. Most of the reactions were grade 1-2 and were transient in nature and no patient discontinued the drug.

Conclusions

The current results indicate that PTG-300 is an effective agent for the treatment of PV, reversing iron deficiency and eliminating the need for TP in PV patients. Elimination of TP requirements for 7 months in TP-dependent PV patients is significant and unexpected. The effect of PTG-300 on PV-related symptoms is also being evaluated. Continued patient enrollment will enable more definitive conclusions regarding the efficacy and safety of hepcidin mimetic PTG-300 in PV patients with high TP requirements. PTG-300 looks very promising in eliminating the therapeutic phlebotomies in both low and high-risk patients.



* Titrate every 4 weeks to maintain hematocrit <45%.

Figure 1: Trial Design

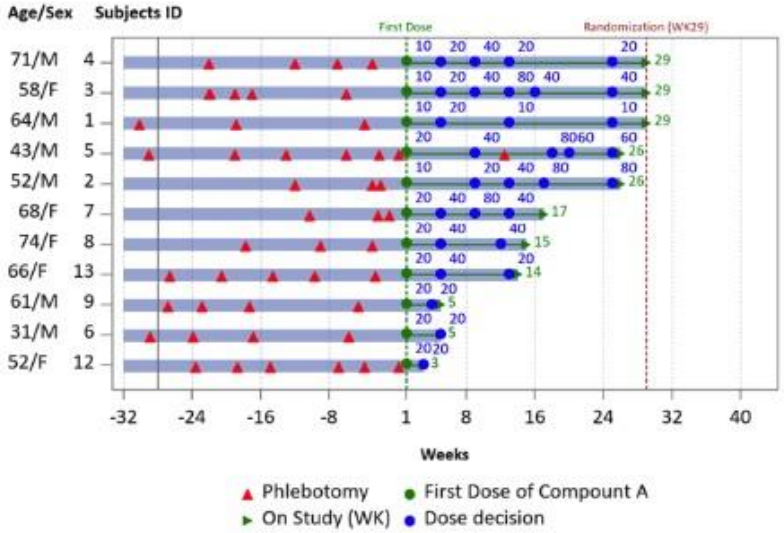


Figure 2a: Reduction in phlebotomies in PV subjects during treatment with PTG-300.

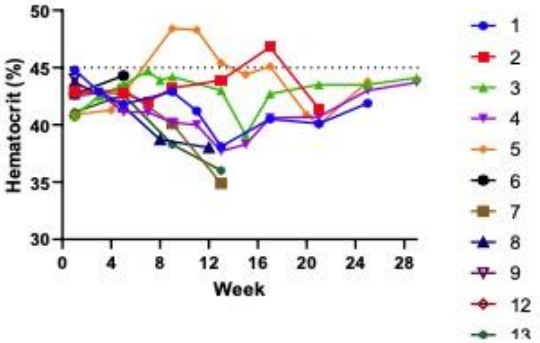


Figure 2b: Improved hematocrit control in PV subjects during treatment with PTG-300.

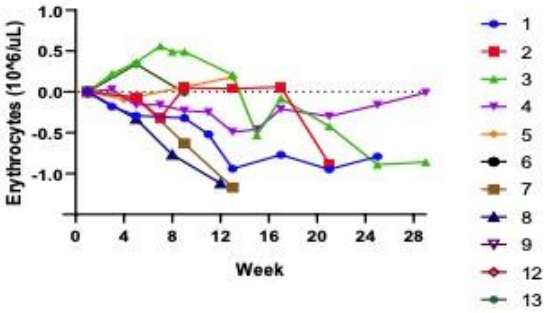


Figure 2c: Change in erythrocytes from baseline in PV subjects during treatment with PTG-300.