Rusfertide (PTG-300) Treatment Interruption Reverses Hematological Gains and Upon Reinitiation, Restoration of Clinical Benefit is Observed in Patients With Polycythemia Vera

Naveen Pemmaraju[1], Andrew Kuykendall[2], Marina Kremyanskaya[3], Yelena Ginzburg[3], Ellen Ritchie[4], Jason Gotlib[5], Aaron Gerds[6], Jeanne Palmer[7], Frank Valone[8], Paula O Connor[8], Nishit B Modi[8], Suneel Gupta[8], Ronald Hoffman[3], Srdan Verstovsek[1]

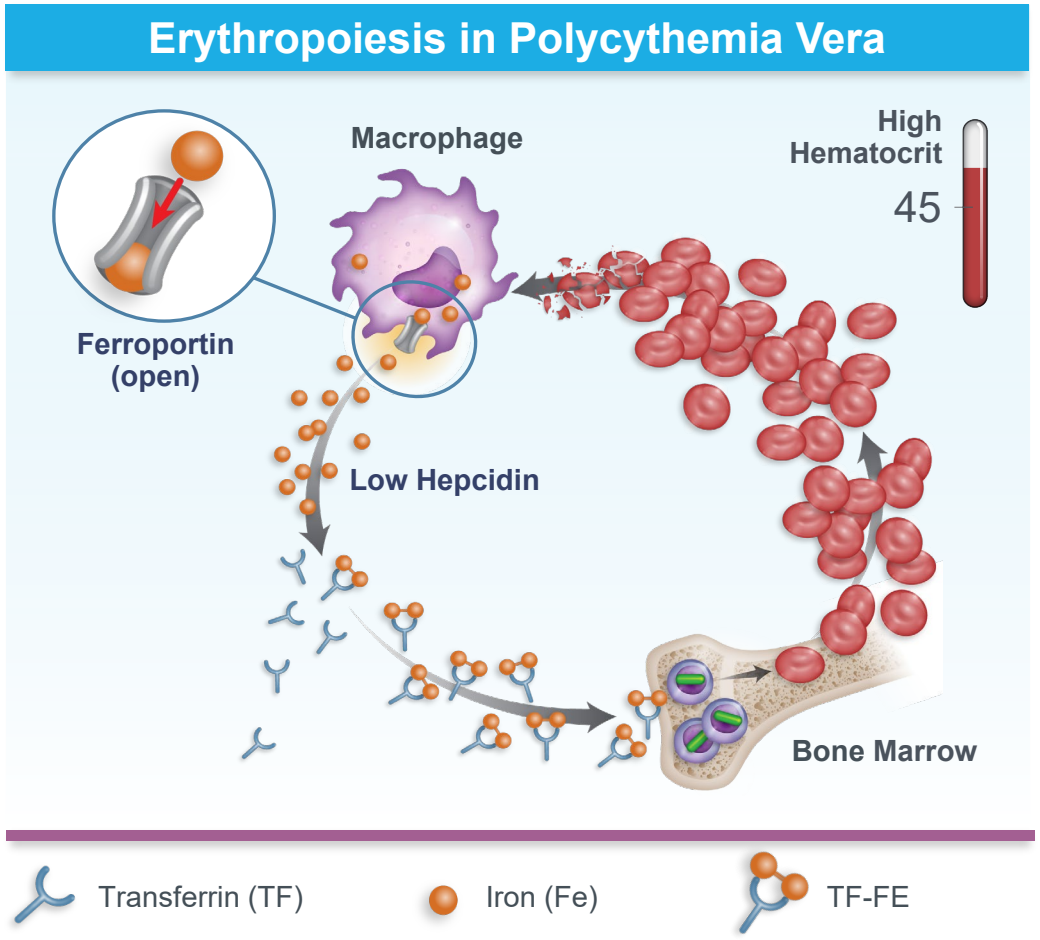
1. MD Anderson Cancer Center, Houston, TX, USA; 2. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA; 3. Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA; 4. New York-Presbyterian Hospital- Weill Cornell Medical College of Cornell University, New York, NY, USA; 5. Stanford Hospital, Palo Alto, CA, USA; 6. Cleveland Clinic Taussig Cancer Center, Cleveland, OH, USA; 7. Mayo Clinic Hospital, Phoenix, AZ, USA; 8. Protagonist Therapeutics, Inc, Newark, CA, USA

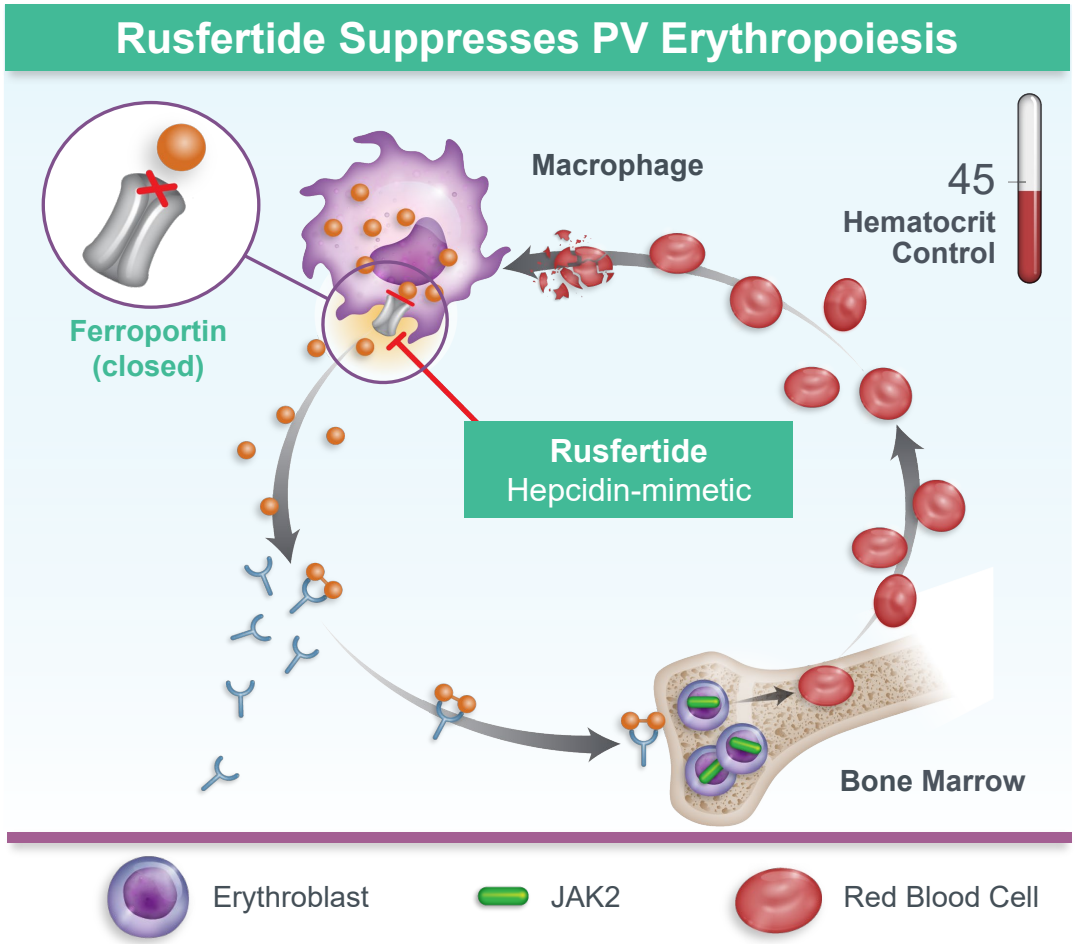
Background: Rusfertide (PTG-300)

- Polycythemia vera (PV) is characterized by excessive red blood cell production and is associated with an increased risk of mortality due to thrombotic events when HCT levels are not controlled at <45%[1]
- PV is generally not optimally managed in most clinical settings[2]
  - In a 2-year period, only 22% of patients had HCT <45% on all tests; 49% had HCT >50% at least once[2]
  - Phlebotomy and cytoreductive therapies (e.g., hydroxyurea, ruxolitinib, and interferons) are not uniformly effective or tolerable
- PV is associated with suppression of hepcidin, in part, due to erythroid hyperplasia and iron deficiency[3]
- Rusfertide, a hepcidin mimetic, is being developed for patients with PV and uncontrolled erythrocytosis despite standard therapy
- REVIVE (NCT04057040) is a phase 2 clinical trial investigating rusfertide + therapeutic phlebotomy ± cytoreductive therapy in patients with phlebotomy-dependent PV

1. Marchioli R, et al. *N Engl J Med*. 2013;368:22–33; 2. Verstovsek S, et al. *Blood*. 2020;136 (Supplement 1): Abstract 2998; 3. Ginzburg YZ, et al. *Leukemia*. 2018;32:2105–2116.

Rationale for using Hepcidin-Mimetics (Rusfertide) in PV





REVIVE Study Design

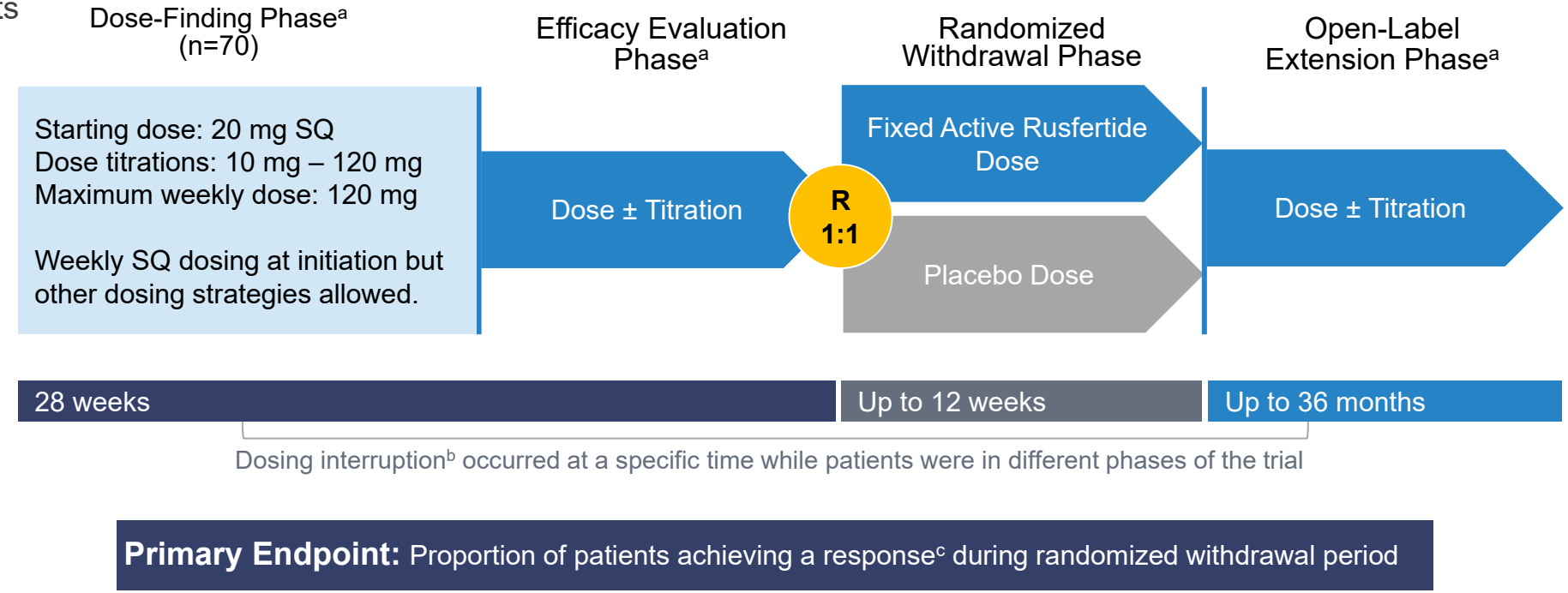
First patient enrolled in October 2019, and last patient enrolled March 2022

ELIGIBILITY REQUIREMENTS:

- Phlebotomy-dependent PV patients diagnosed per 2016 WHO criteria
- ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
- All patients prior to first rusfertide dose were phlebotomized to HCT <45% to standardize the starting HCT
- Rusfertide doses of 10–120 mg administered subcutaneously added to prior standard therapy

ADD-ON STUDY DESIGN

Clinical Goal: To maintain HCT <45%



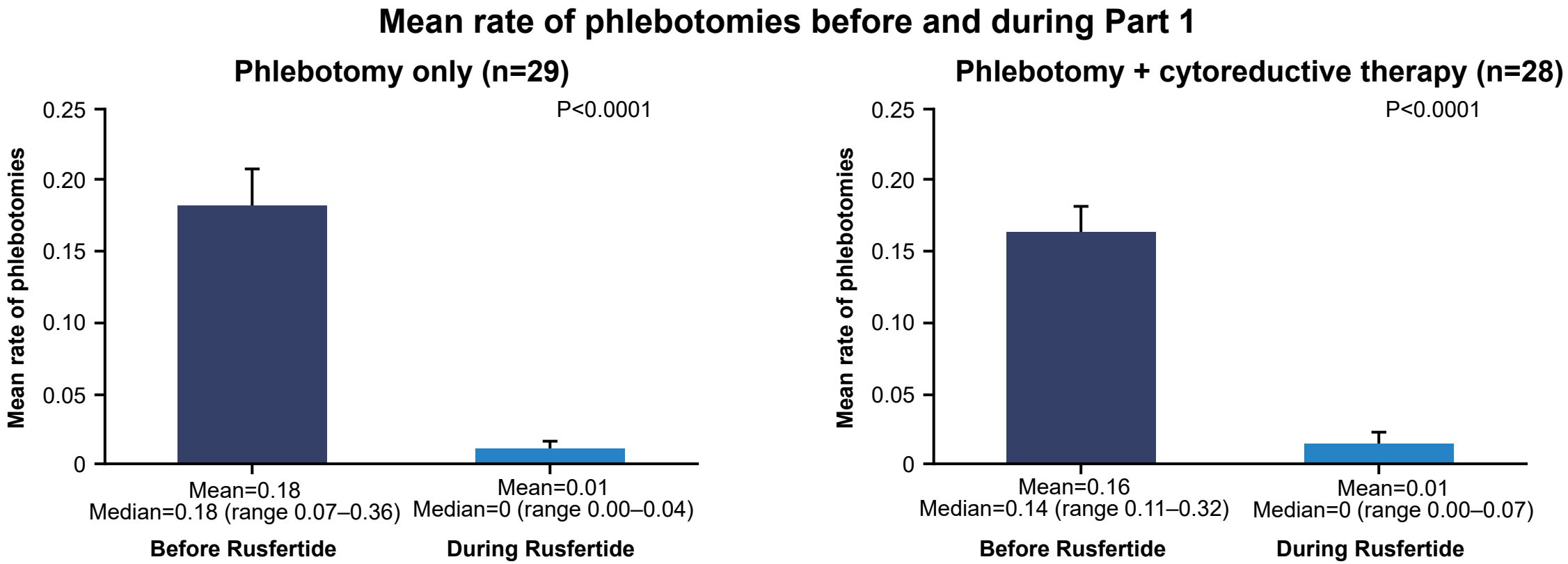
Dosing interruption[b] occurred at a specific time while patients were in different phases of the trial

Primary Endpoint: Proportion of patients achieving a response[c] during randomized withdrawal period

[a]Titrate every 4 weeks to maintain HCT <45%. [b]Dosing interruptions were due to clinical hold and not protocol-defined. [c]Response defined as having achieved the absence of "phlebotomy eligibility", or HCT >45% that was ≥3% higher than baseline or HCT >48%, during the efficacy evaluation phase beginning Week 17 and continuing to Week 29.
CRT, cytoreductive therapy; HCT, hematocrit; PV, polycythemia vera; SQ, subcutaneous; WHO, World Health Organization. ClinicalTrials.gov Identifier: NCT04057040

Rusfertide Significantly Decreased Phlebotomy Requirements in Patients Treated With Phlebotomy Only or Cytoreductive Therapy Plus Phlebotomy

- Number of phlebotomies in 28 weeks before treatment with rusfertide: mean 4.81 (median 4; range 2–10)
- Number of phlebotomies after starting rusfertide: mean 0.30 (median 0; range 0–2)



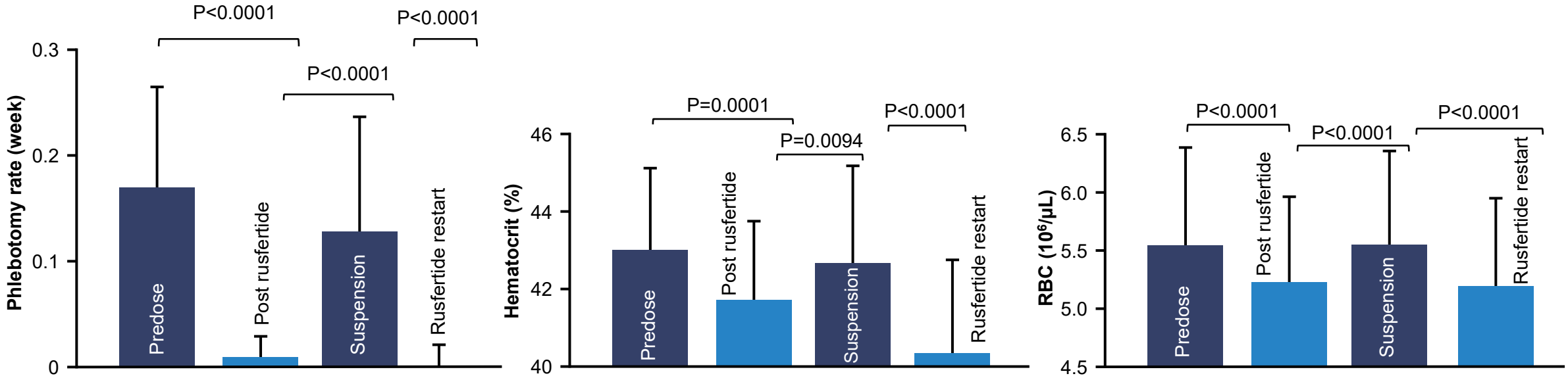
Data cutoff: May 11, 2022. Phlebotomy requirements are available for 57 patients who completed the first 28 weeks of dosing.

Note: Error bars indicate 95% confidence intervals for the mean.

Rusfertide Treatment Interruption Leads to Loss of Effect and Rusfertide Restart Restores Effect

- During the brief clinical hold in response to nonclinical rasH2 mouse model findings, patients were maintained on their cytoreductive regimens and had TP for HCT >45%
- The study protocol was amended to add this information, dermatological screening, and stopping rules. Rusfertide was reinitiated following patient reconsent
- Most patients (85%) returned to rusfertide add-on treatment 2-3 months after the dosing interruption and reinitiation

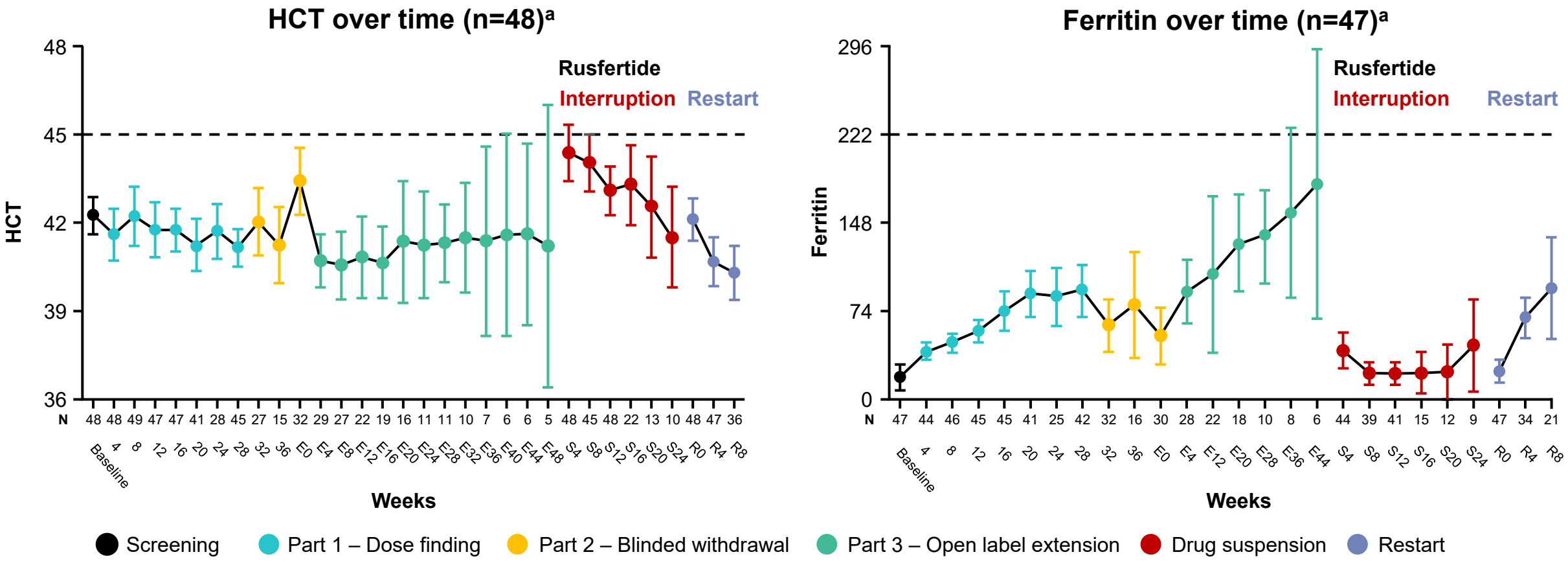
Clinical effect (n=48)[a]



Data cutoff: May 11, 2022

[a]Patients with complete restart data.

Rusfertide Treatment Interruption Leads to Loss of Effect on Hematocrit and to Decreased Ferritin

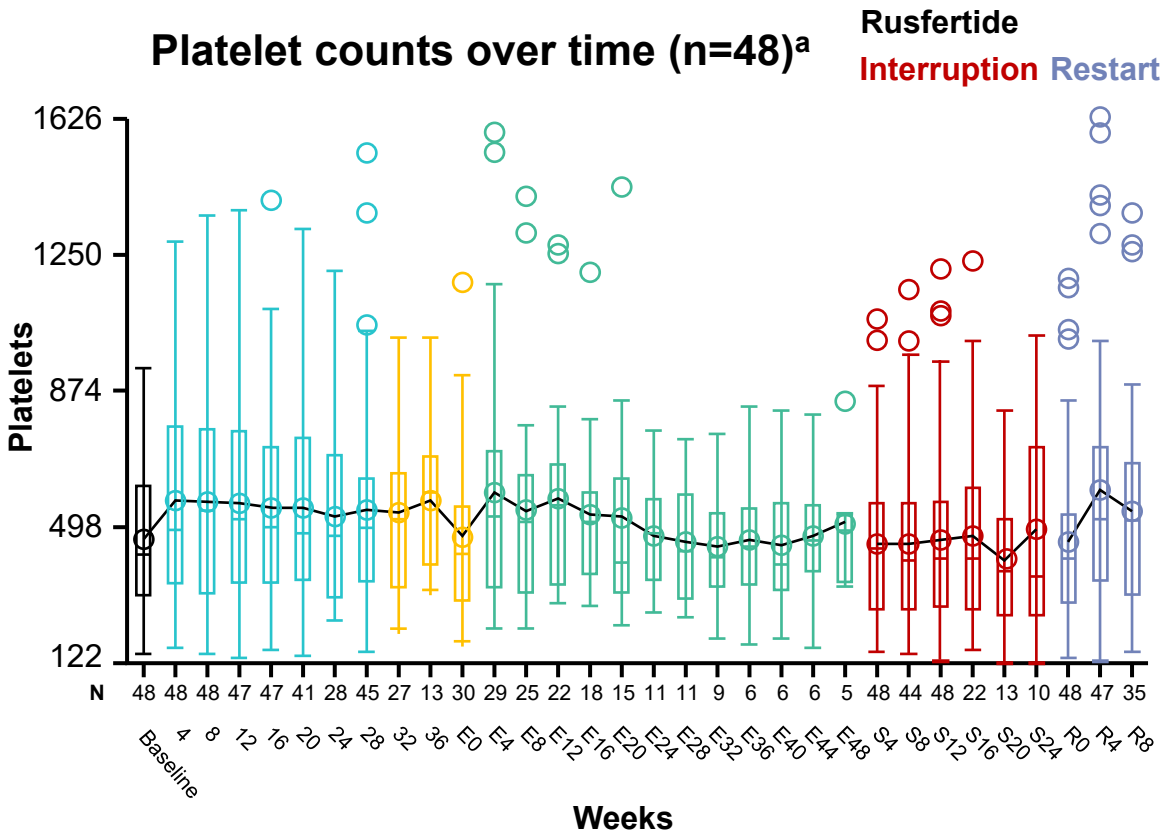


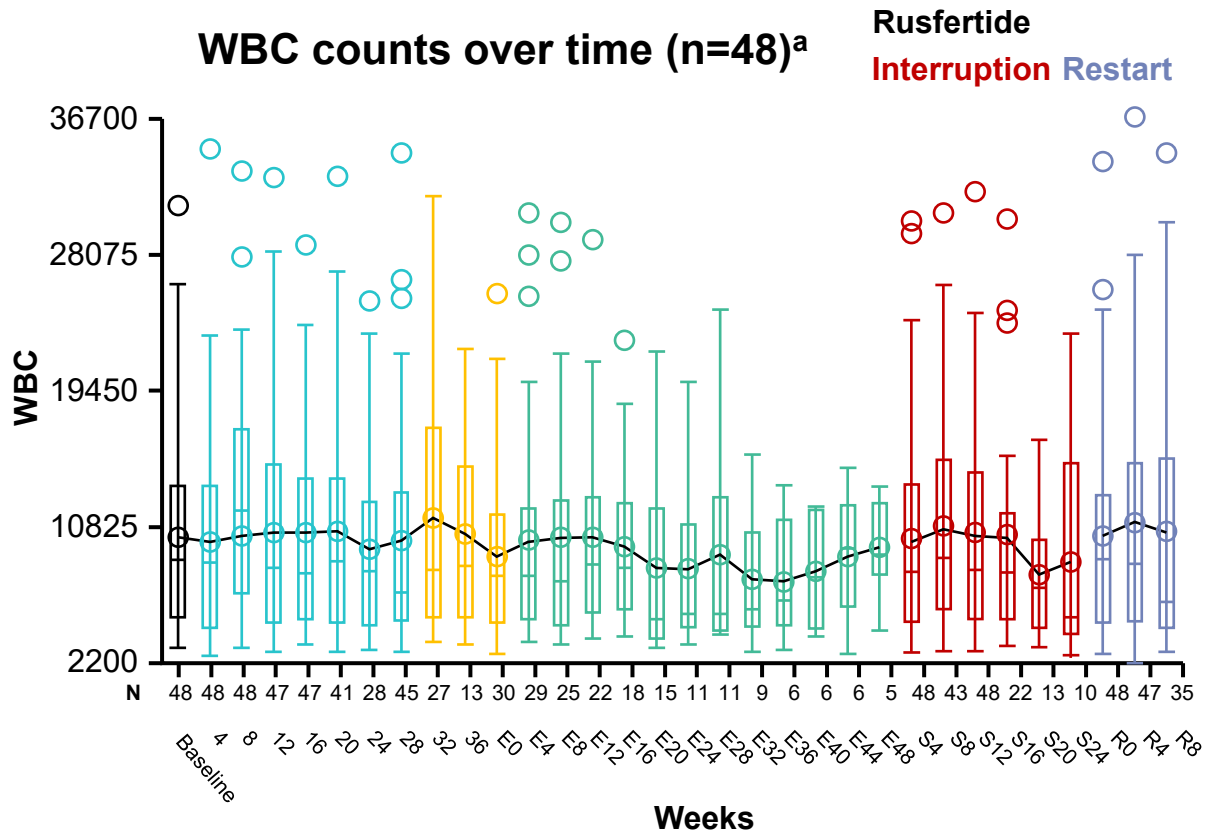
A similar pattern was observed with RBC counts

Data cutoff: May 11, 2022

[a]Patients with complete restart data.

Rusfertide Treatment Interruption Was Associated with No Change in Platelet or Leukocyte Counts





Screening | Part 1 – Dose finding | Part 2 – Blinded withdrawal | Part 3 – Open label extension | Drug suspension | Restart

Data cutoff: May 11, 2022

[a]Patients with complete restart data.

Safety: Rusfertide (PTG-300)

- Most treatment-emergent adverse events (TEAEs) were grade 1-2
  - Injection site reaction (ISRs) were the most common AE and occurred in 80% of patients. All ISRs were transient, and no patient discontinued due to an ISR
- No grade 3 events related to rusfertide
- No grade 4 or 5 TEAEs
- 3 withdrawals due to TEAEs
  - 1 AML, 1 thrombocytosis (Grade 1), and 1 pulmonary embolism identified on study
- Secondary malignancies
  - 5 patients (5.5%) had secondary malignancies (6 skin cancers [3 SCC, 2 basal cell, 1 MM] 1 AML) in all rusfertide-treated patients in phase 2 trials (N=90)
  - All skin cancers were in situ or stage 1
  - All newly developed cancers were in patients with previous rux and/or HU. The patient with AML had also experienced radioactive iodine exposure

Any-grade TEAE in ≥10% (preferred term)	n (%)
Total number of patients	**70**
Injection site reaction	56 (80)
Fatigue	19 (27.1)
Pruritus	17 (24.3)
Arthralgia	16 (22.9)
Headache	15 (21.4)
Dizziness	13 (18.6)
Nausea	12 (17.1)
Anemia	11 (15.7)
Hyperhidrosis	9 (12.9)
Diarrhea	8 (11.4)
Insomnia	8 (11.4)
Dyspnea	8 (11.4)
COVID-19	7 (10)
Hyperuricemia	7 (10)
Pain in extremity	7 (10)

Data cutoff: May 11, 2022

Conclusions: Rusfertide (PTG-300)

- PV patients with erythrocytosis requiring frequent phlebotomy + cytoreductives were treated with rusfertide for up to 18 months
- Rusfertide therapy resulted in rapid, sustained, and durable hematocrit control without clinically meaningful increases in WBC numbers, platelet counts. or PV-related thromboses. Patients have been treated up to 1.5 years with the patients remaining essentially phlebotomy-free
- Rusfertide demonstrated similar efficacy in all categories of patients, independent of the PV patient risk category or concurrent therapy with hydroxyurea, interferon, or ruxolitinib
- Rusfertide appears well tolerated with Grade 1-2 ISRs being the most frequent AE. The number of patients with secondary malignancy was consistent with previous reports in the PV population
- Rusfertide dosing was suspended, due to a clinical hold and dosing was resumed subsequently. Treatment suspension led to loss of benefit (e.g., increased phlebotomy rate, increased HCT, decreased ferritin). Rusfertide restart restored therapeutic benefits

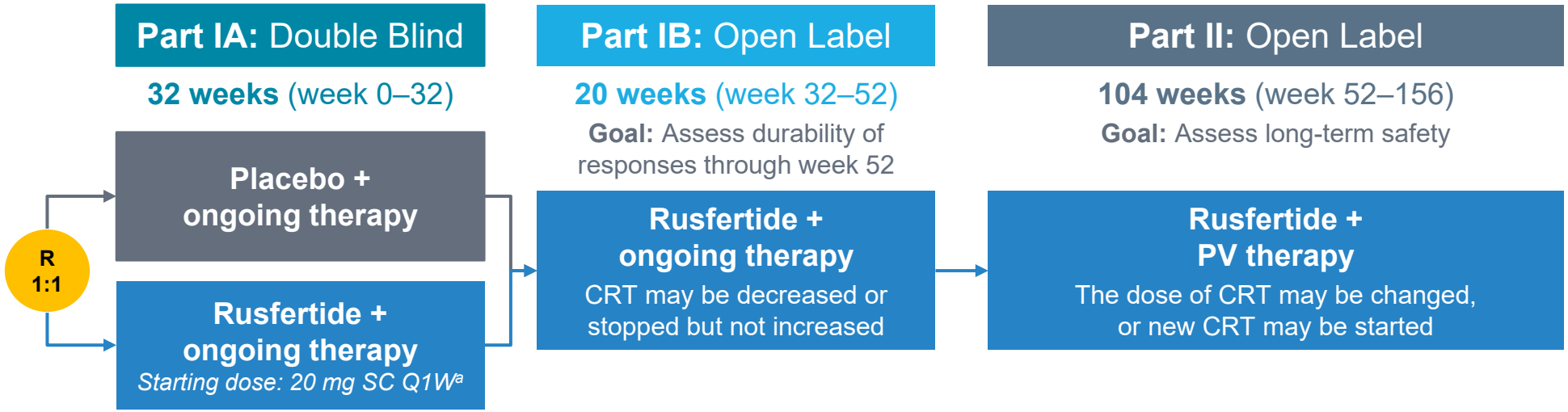
Phase 3 Study: VERIFY (NCT05210790)

250 PV patients to be randomized across 100 global sites — Now enrolling

Key Eligibility:

- Age ≥18 years
- Meet revised WHO criteria for diagnosis of PV and JAKV617F or exon 12 mutation
- ≥3 phlebotomies due to inadequate HCT in 6 months OR ≥5 phlebotomies within 1 year of randomization
- If receiving CRT, stable dose PV regimen
- If phlebotomy alone, must have stopped CRT 2-6 months before screening

N=250



Primary Endpoint:

Proportion of patients achieving response[b] week 20–32

[a]Doses >60 mg require 2 injections; dose titrations are 20 mg, 30 mg, 45 mg, 60 mg, 75 mg, and 90 mg. Maximum dose/day is 90 mg; maximum dose per week is 90 mg in Parts 1A and 1B and 120 mg in Part 2.
[b]Response defined as absence of phlebotomy eligibility. Phlebotomy eligibility is defined as a confirmed HCT ≥45% and that is at least 3% higher than the baseline OR HCT ≥48%. CRT, cytoreductive therapy.
ClinicalTrials.gov Identifier: NCT05210790

Thank you and acknowledgments

We thank the patients who participated in the study and their caregivers, as well as the investigators and clinical research staff from the study centers

---

This study was sponsored by Protagonist Therapeutics, Inc.