2022 ASCO® ANNUAL MEETING

Rusfertide (PTG-300) Treatment in Phlebotomy-Dependent Polycythemia Vera

Ronald Hoffman, Yelena Ginzburg, Marina Kremyanskaya, Sarita Khanna, Nishit Modi, Frank Valone, Paula O'Connor, Suneel Gupta, Samuel R. Saks

The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York; Protagonist Therapeutics, Newark, CA.

Conflict of Interest

Hoffman: Consultant to Dompe, Scholar Rock, Incyte, Novartis, Kartos, Turning Point Therapeutics, Abbvie, Protagonist Therapeutics

Kremyanskaya – Consultant to Incyte, Morphosys, Protagonist

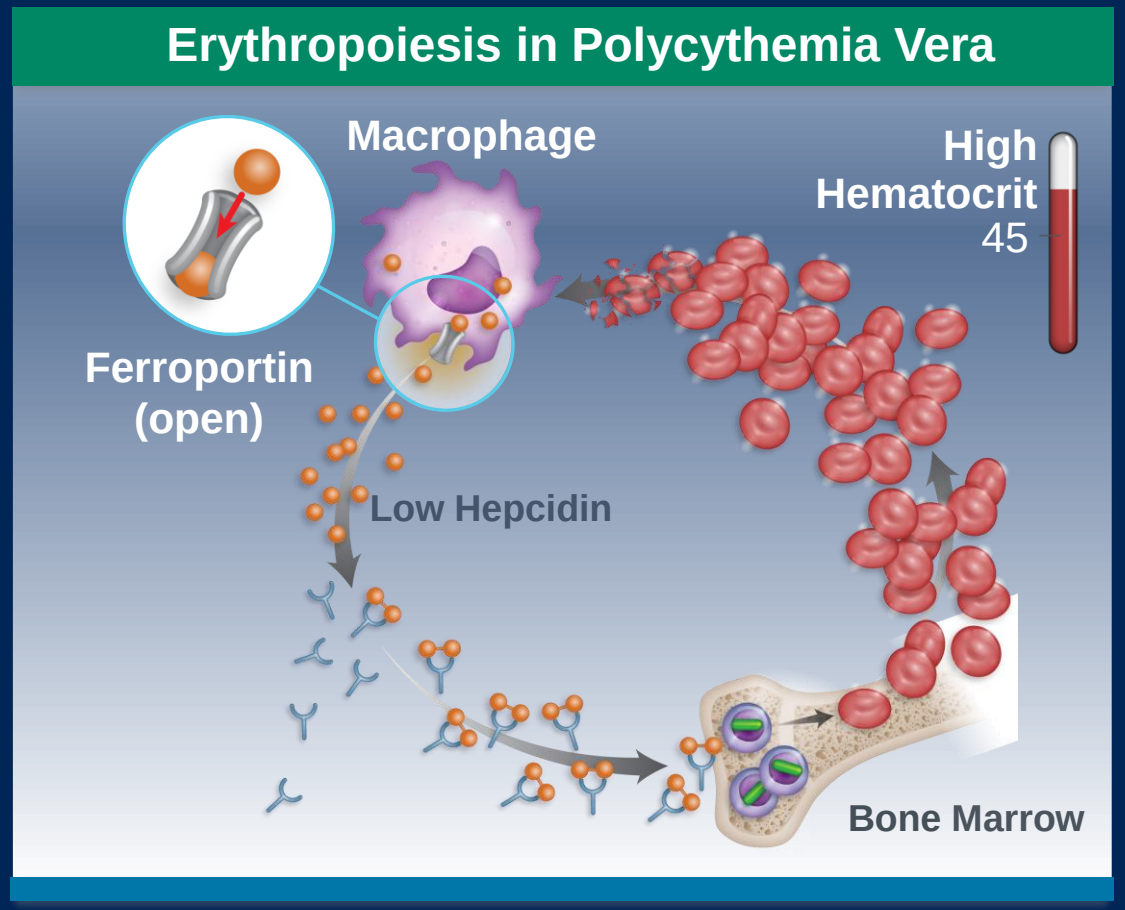
Ginzburg: Consultant to Protagonist, Ionis, Takeda, and Repare; research funding from Protagonist and Repare

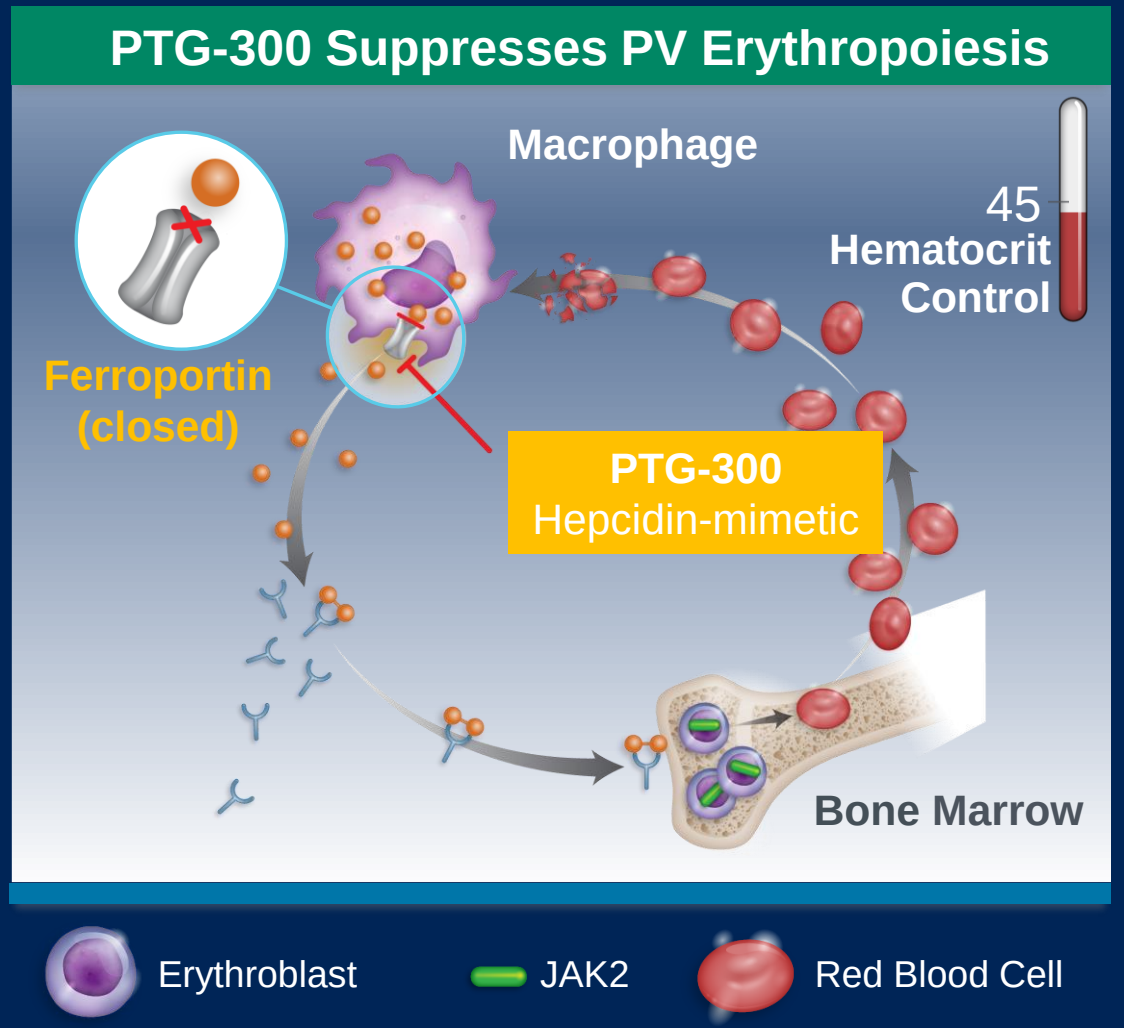
Gupta, O'Connor, **Valone, Khanna, Modi, Saks:** Employees or consultants of Protagonist and are Protagonist shareholders.

Background

- Polycythemia vera (PV) is a serious disease characterized by excessive red blood cell production and associated with an increased risk of morbidity and mortality when hct levels are not controlled at <45% (Marchioli et al, NEJM 2013)
- Current therapies, phlebotomy and cytoreductive therapies (hydrea, ruxolitinib, and interferons) are not uniformly effective or tolerable
- PV disease symptoms may be/are exacerbated by phlebotomy related iron deficiency
- Rusfertide, a hepcidin mimetic, is a novel molecule being developed as a potential therapy PV associated erythrocytosis for PV subjects with uncontrolled erythrocytosis despite standard therapy
- Two proof of concept studies, REVIVE and PACIFIC, have been conducted and preliminary data presented. We will update the REVIVE data, specifically touching upon data collected during a mandated dosing suspension in response to a pre-clinical safety finding and discuss the potential role for rusfertide in PV
- **PV as compared to secondary forms of erythrocytosis is associated with relative suppression of hepcidin potentially due to greater degrees of expanded erythropoiesis and iron deficiency (Ginzburg / Hoffman Leukemia 2018)**
- Erythrocytosis in PV occurs despite iron deficient erythropoiesis

Rationale for Using a Hepcidin-Mimetic (PTG-300) in PV





PRESENTED BY:
Ron Hoffman. Abstract # 7003

REVIVE (Phase 2) Trial of Rusfertide in PV Patients (n=70)

ELIGIBILITY REQUIREMENTS:

Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria

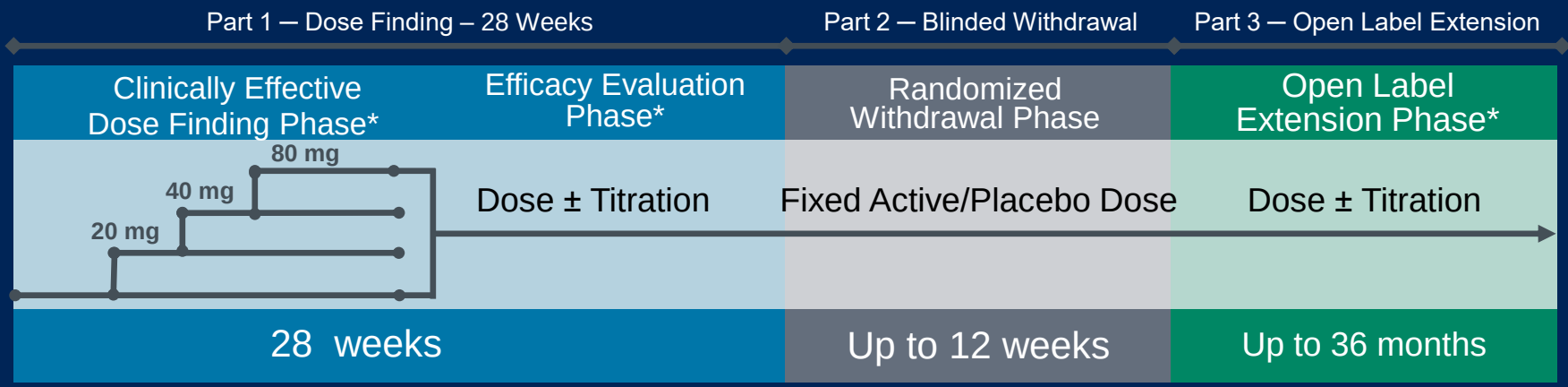
≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy

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 weekly added to prior standard therapy

ADD-ON STUDY DESIGN

Clinical GOAL: To maintain hematocrit <45%



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

First patient enrolled in Oct, 2019 and Last patient enrolled May 2021

Baseline Characteristics in REVIVE Study

Characteristics (n = 70)

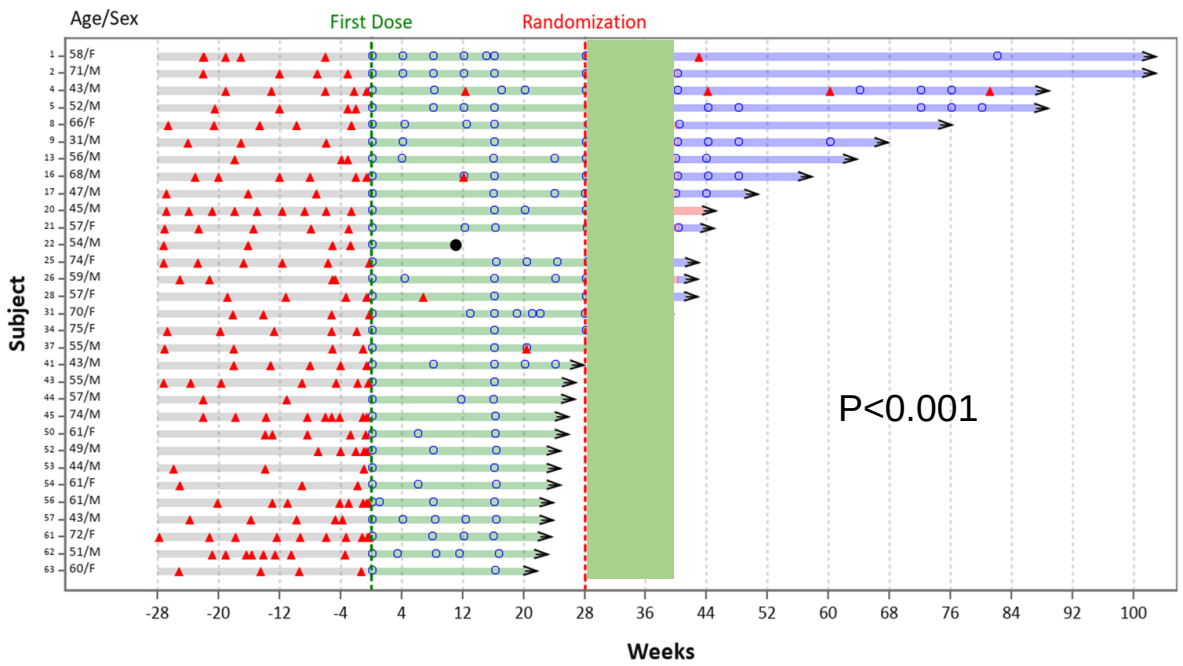
AGE	
Range	27-77 years (Mean = 57.3 yrs)
GENDER	
Females	21 (30.0%)
Males	49 (70.0%)
RISK	
Low	29 (41.4%)
High	41 (58.6%) [Age based – 37.1%, Thrombotic events – 21.4%]
DURATION SINCE PV DIAGNOSIS	
<1 yr	14 (20.0%)
1 - <3 yrs	24 (34.3%)
3 - <5 yrs	11 (15.7%)
≥5 yrs	21 (30.0%)

Data as of March 10, 2022

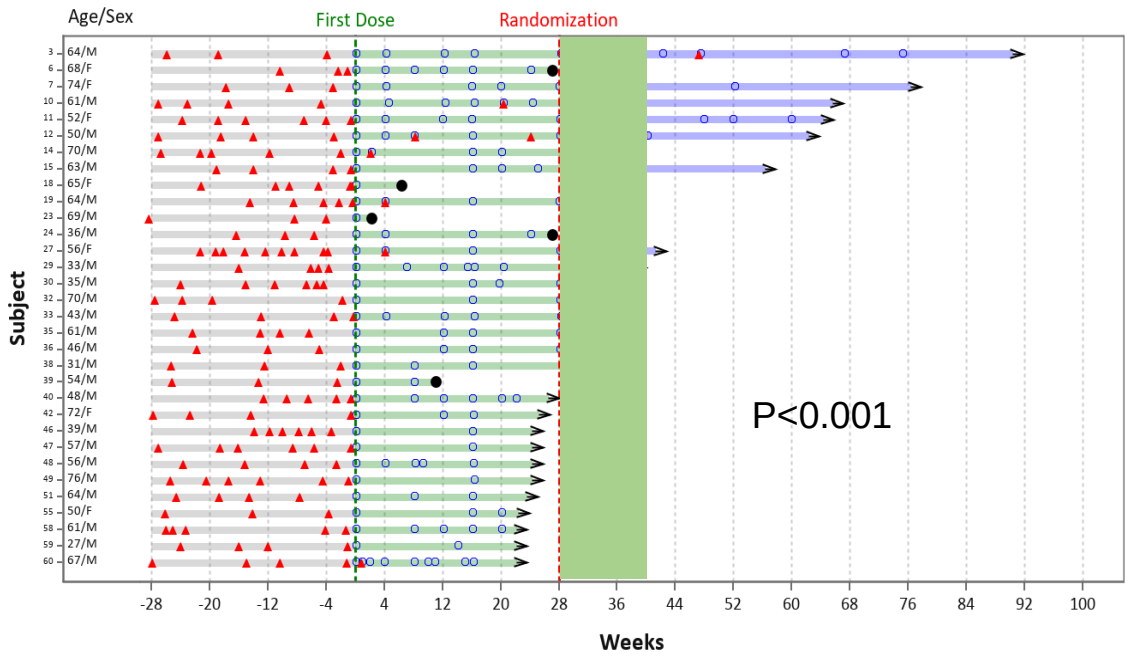
THERAPIES	
PHL only	34 (48.6%)
PHL + HU	21 (30.0%)
PHL + IFN	8 (11.4%)
PHL + RUX	3 (4.3%)
PHL +Multiple Agents	4 (5.7%)
NUMBER OF PHL IN 28 WEEKS PRIOR	
2-3	14 (20.0%)
4-5	38 (54.3%)
≥6	18 (25.7%)
Range	4.79
DAYS BETWEEN PHLEBOTOMIES	
Median	34

Effect of Rusfertide on Reducing Phlebotomy Frequency

PHLEBOTOMY ONLY (N=31, 49%)



PHLEBOTOMY + CYTOREDUCTIVE (N=32, 51%)



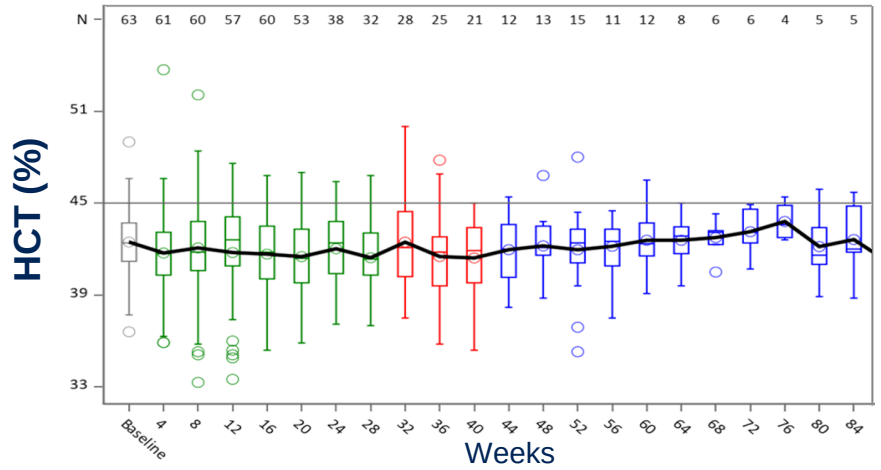
Median Dose 40-60 mg/week

During the first 28 weeks of treatment, **84% of patients did not require a phlebotomy,** 14% required one and 2% required two phlebotomies.

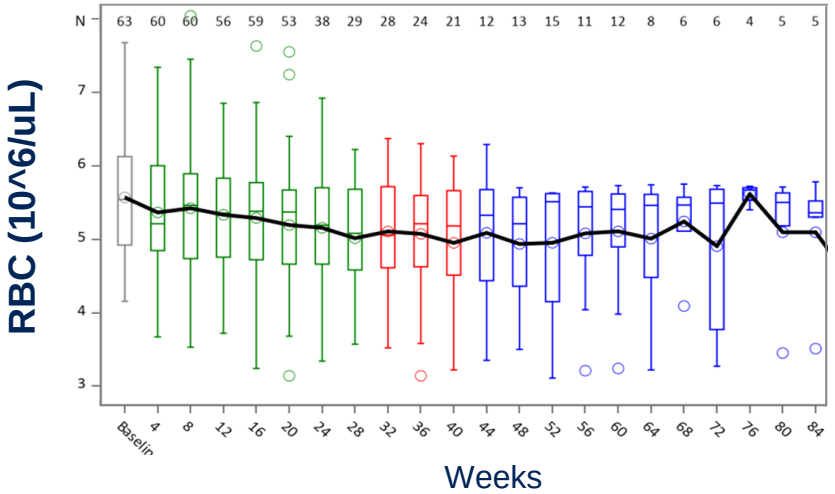
Data cut off Sept 30, 2021

Effect of Rusfertide on HCT, RBC, WBC, Platelets

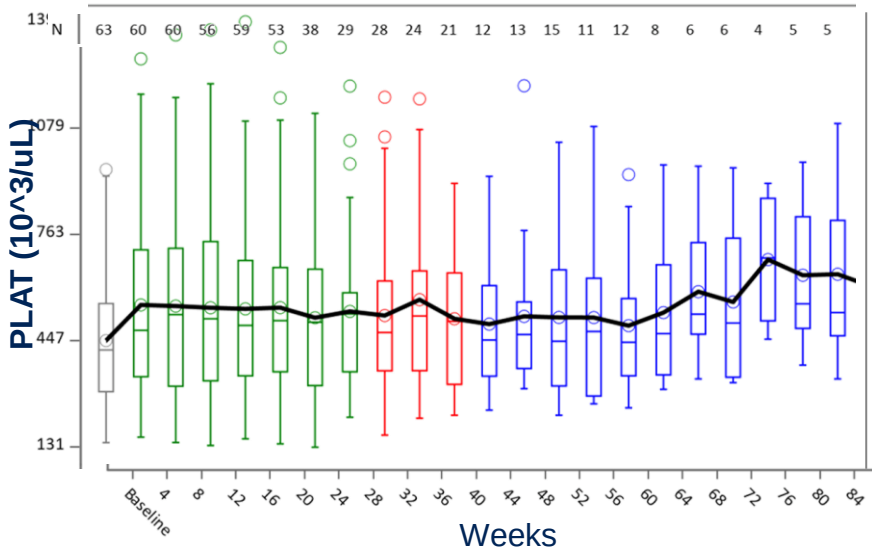
RUSFERTIDE CONTROLS HCT



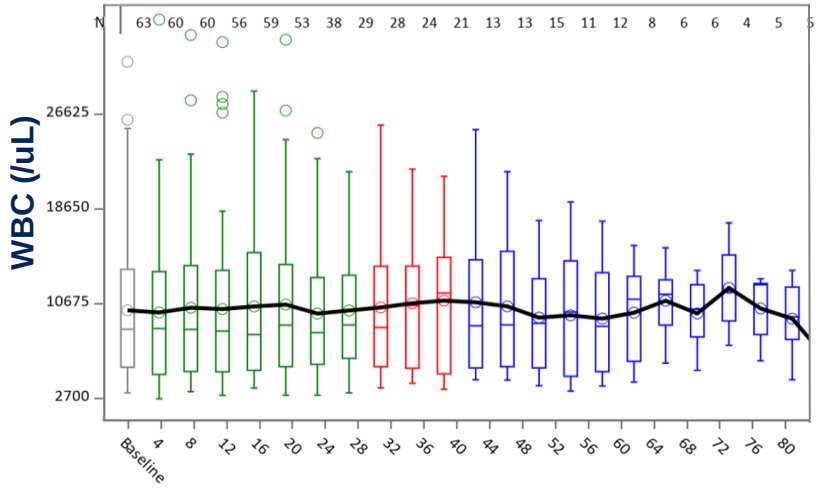
RUSFERTIDE REDUCES RBC COUNT



NO CLINICALLY SIGNIFICANT CHANGES IN PLATELETS



NO CLINICALLY SIGNIFICANT CHANGES IN WBC



Screening

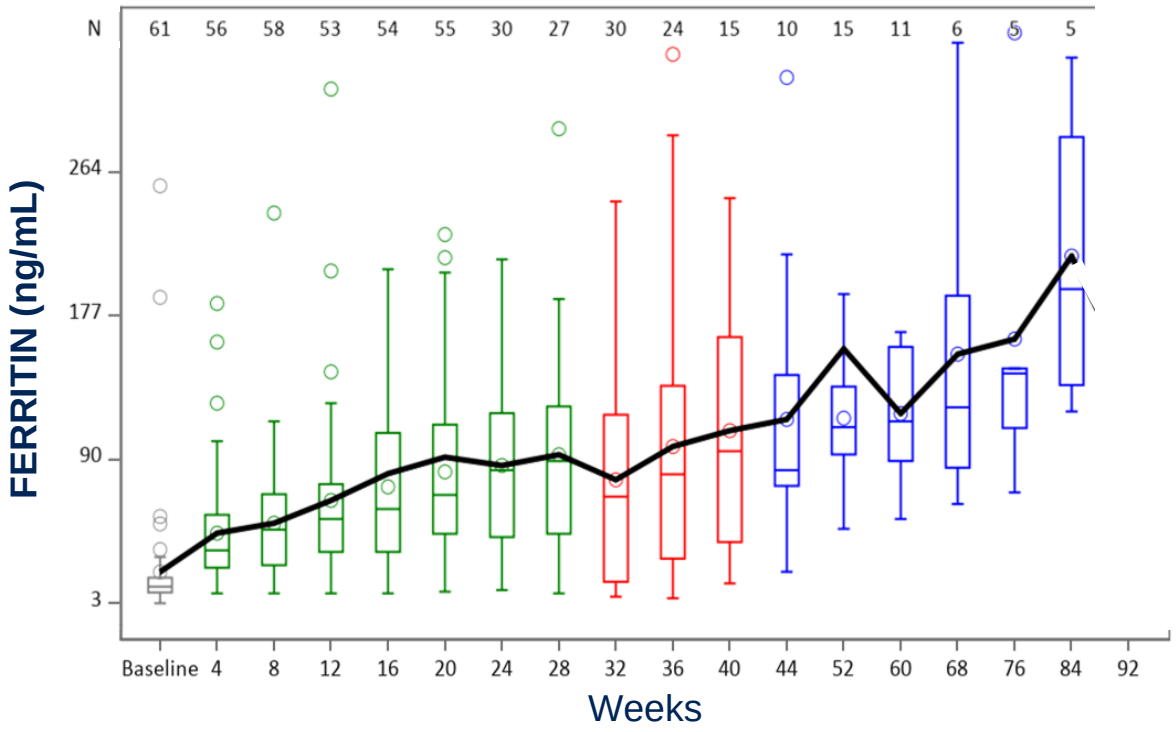
Part 1 – Dose Finding

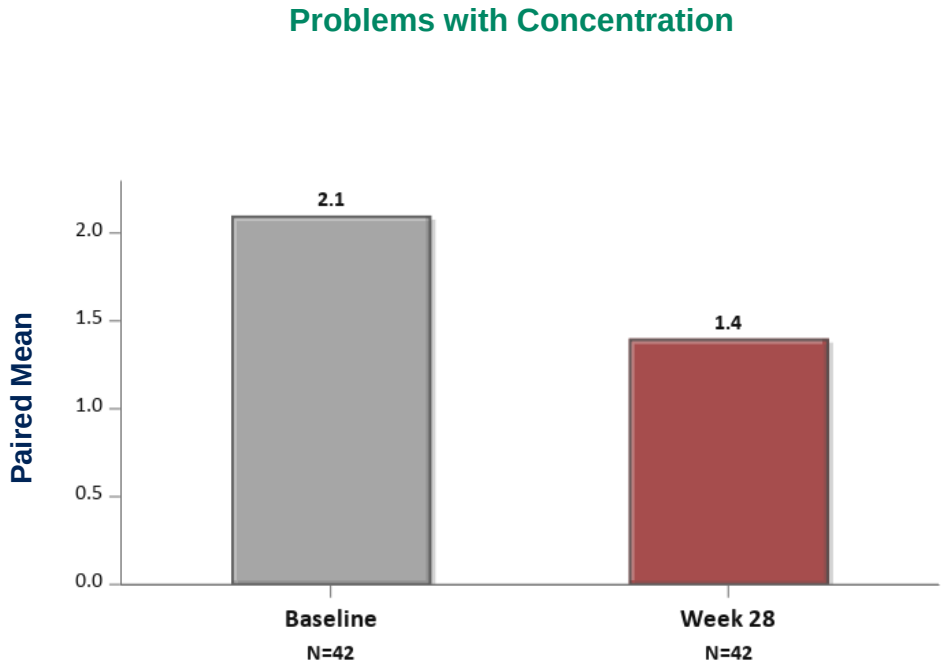
Part 2/3 – Blinded Withdrawal/OLE

Part 3 – Open Label Extension

Data cut off Sept 30, 2021

Rusfertide Normalizes Iron Stores and Improves Symptoms





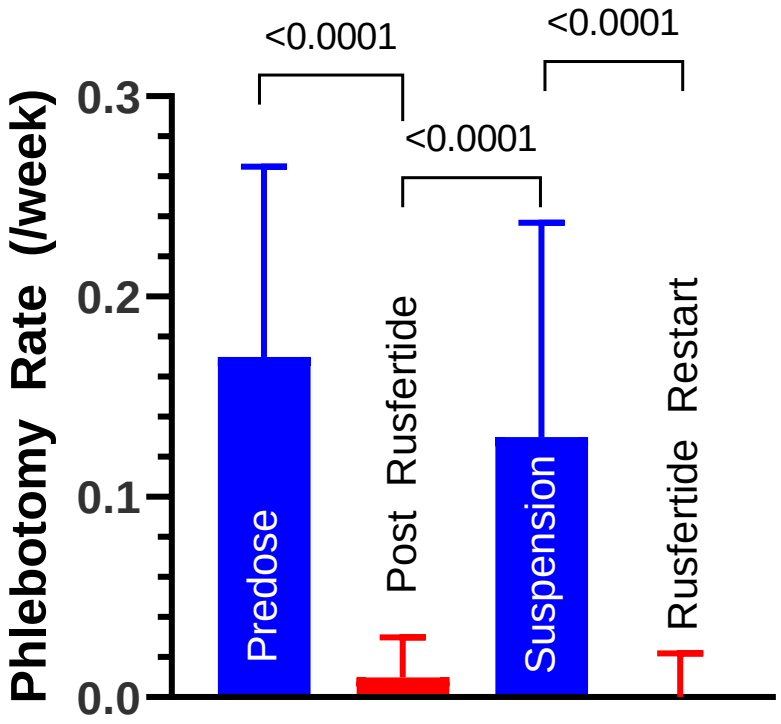
Screening Part 1 – Dose Finding Part 2/3 – Blinded Withdrawal/OLE

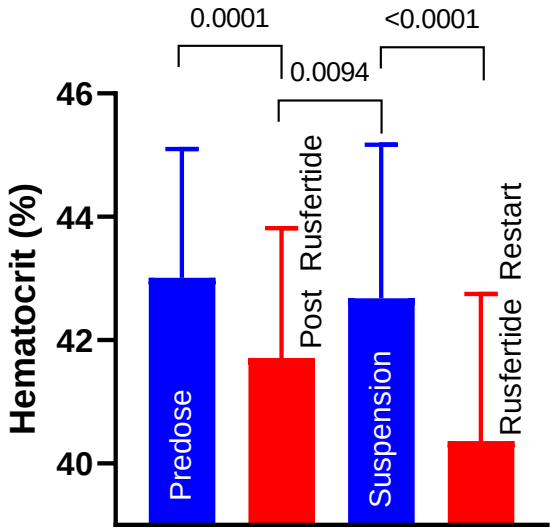
Part 3 – Open Label Extension

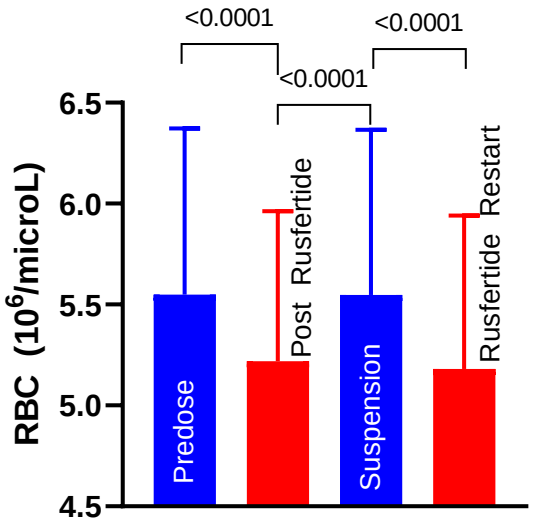
Data cut off Sept 30, 2021

Rusfertide Treatment Suspension leads to Loss of Effect (n=48)

Treatment Restart Restores Benefit





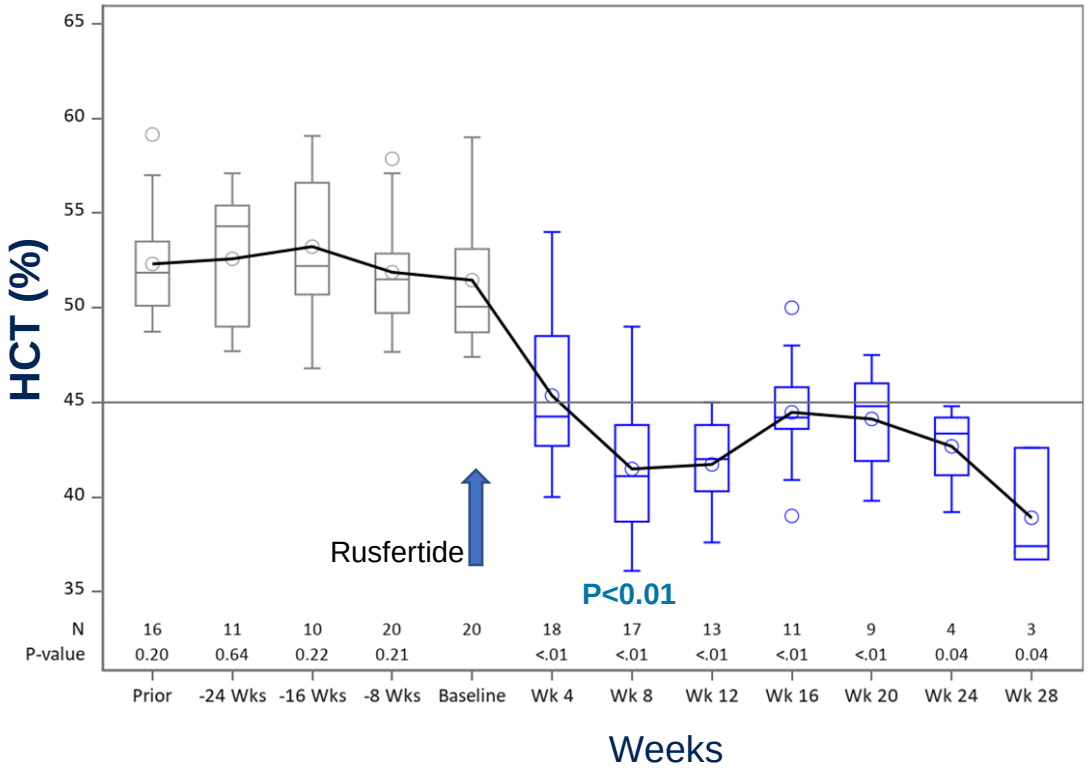


- Dosing suspension (Sept- Dec 2021) in response to pre-clinical findings in rash2 mouse carcinogenicity model. 85% of patients resumed treatment with rusfertide following mandated dosing suspension

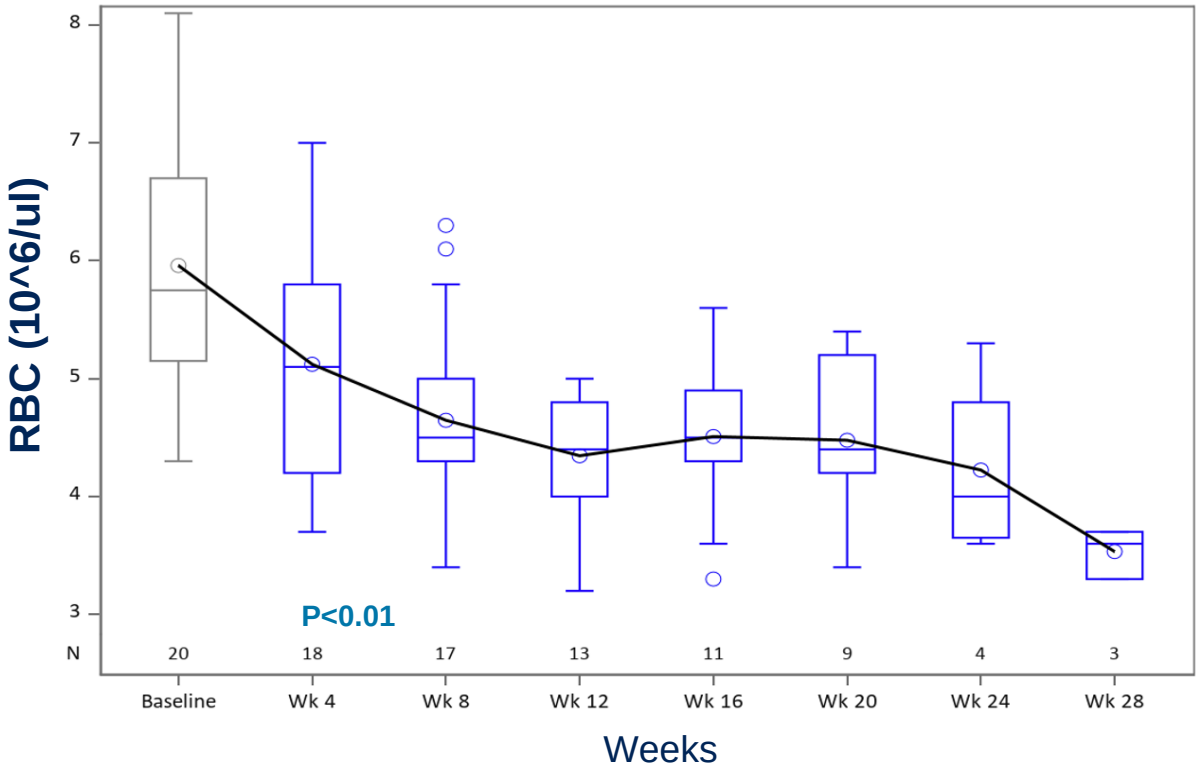
Data cut off May 11, 2022

PACIFIC Study in PV Patients with High (>48%) Baseline Hematocrit (n=20)

RUSFERTIDE IMMEDIATELY CONTROLS HCT



RUSFERTIDE IMMEDIATELY REDUCES RBC COUNT



Screening PTG-300 MEAN

Data cut off Sept 30, 2021

Adverse Events Following Rusfertide in Patients with PV

Most treatment related AEs were Grade 1 or 2

- Injection site reaction (ISRs) were most common and associated with 33% of injections. All ISRs were transient, and no patient discontinued due to an ISR
- **SAE**'s include aneurysm of popliteal artery, atrial fibrillation, chest pain, hydrocephalus, gastroenteritis, syncope, basal cell carcinoma, squamous cell carcinoma, melanoma, AML
- No grade 3 events related to rusfertide
- One grade 4 event possibly related to rusfertide (asymptomatic thrombocytosis of about 1.2 million)
- 2 withdrawals due to possibly related AE - both asymptomatic thrombocytosis (not the grade 4 subject)
- No clinically significant laboratory abnormalities.
- No Anti Drug Antibody response was noted in any patient

System Organ Class Preferred term	AE n (%)
Total number of Subjects	*90*
General disorders and administrative site conditions	77 (85.6)
Fatigue	19 (21.1)
Skin and subcutaneous tissue disorders	37 (41.1)
Pruritis	19 (21.1)
Hyperhidrosis	9 (10.0)
Nervous system disorders	35 (38.9)
Headache	18 (20.0)
Dizziness	14 (15.6)
Gastrointestinal disorders	32 (35.6)
Nausea	13 (14.4)
Diarrhea	11 (12.2)
Musculoskeletal and connective tissue disorders	32 (35.6)
Arthralgia	17 (18.9)
Infections and infestations	23 (25.6)
Investigations	22 (24.4)
Blood and Lymphatic Disorders	20 (22.2)
Anemia	11 (12.2)
Metabolism and nutrition disorders	17 (18.9)
Respiratory, thoracic and mediastinal disorders	16 (17.8)
Injury, poisoning and procedural complications	13 (14.4)
Psychiatric disorders	11 (12.2)
Vascular disorders	9 (10.0)

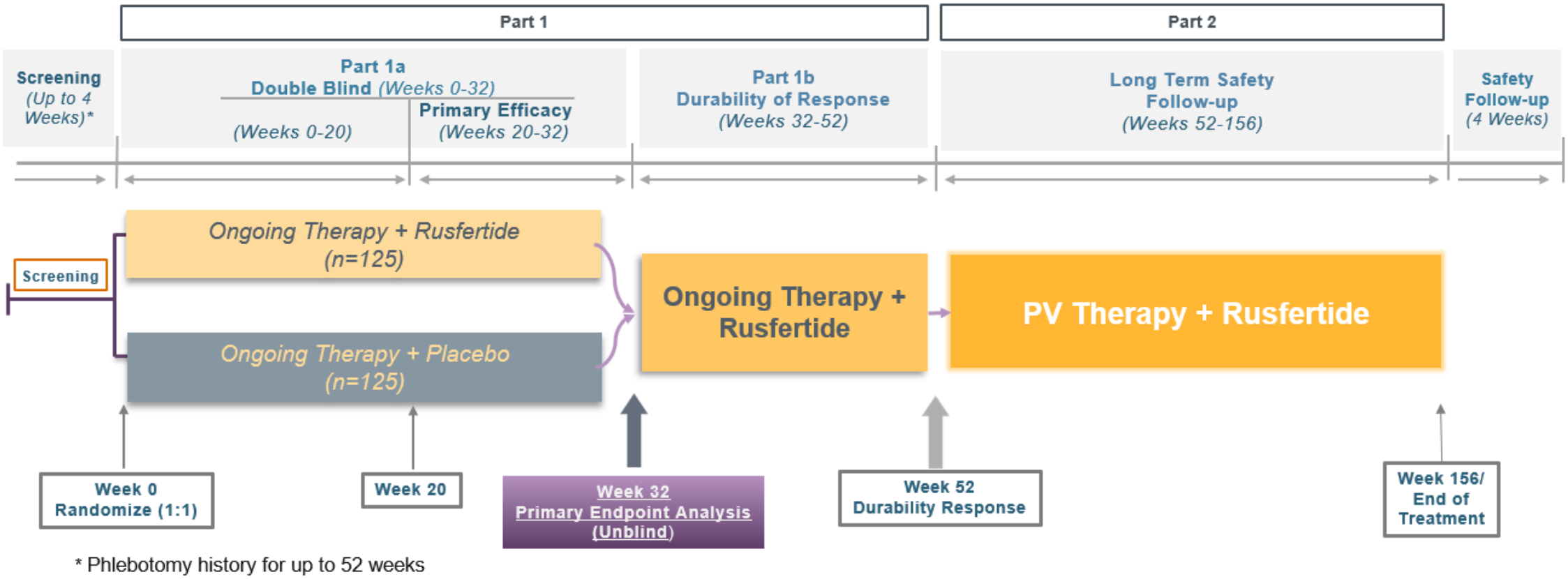
Data Cut Off: Mar 10, 2022

Treatment-emergent AEs with more than 10% incidence

Phase 2 Studies - Conclusions

- Enrollment is complete in Phase 2 studies, dosing ongoing
- 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 an increase in WBC numbers or PV related thromboses. Subjects have been treated up to 1.5 years with the subjects remaining essentially phlebotomy-free
  - Rusfertide induction therapy with twice weekly dosing is effective at rapidly achieving target hematocrit below 45% without phlebotomy in all erythrocytotic PV patients
  - Rusfertide demonstrated similar efficacy in all categories of patients, independent of the PV patient risk category or concurrent therapy with hydroxyurea, interferon or ruxolitinib
  - Safety profile for rusfertide is tolerable
  - Rusfertide dosing was suspended, due to clinical hold and dosing was resumed subsequently. Treatment suspension leads to loss of effect (increased phlebotomy rate, increase in HCT and RBC). Rusfertide restart restored therapeutic benefits

Enrolling Double Blind Placebo-Controlled Phase 3 Study (VERIFY)



* Phlebotomy history for up to 52 weeks

250 PV Patients to be randomized across 100 Global sites- Screening started in Q1, 2022

Thank You

- Thanks to the patients who participated
- Investigators
  - Mt. Sinai, NY: Marina Kremyanskaya, Yelena Ginzburg, Ronald Hoffman
  - MD Anderson, Tx: Naveen Pemmaraju, Srdan Verstovsek
  - Lee Moffitt Cancer Center, FL Andrew Kuykendall,
  - Cancer Center, University of Kansas, KS: Abdulraheem Yacoub,
  - Karmanos Cancer Institute, MI: Jay Yang
  - Stanford University, CA Jason Gotlib
  - Cornell University, NY Ellen Ritchie