Protagonist Therapeutics

ASH 2021 PRESENTATION SLIDES

December 2021

All data current as of ASH cut-off (September 2021)

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Protagonist Therapeutics

Oral Presentation 1

Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients

Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients

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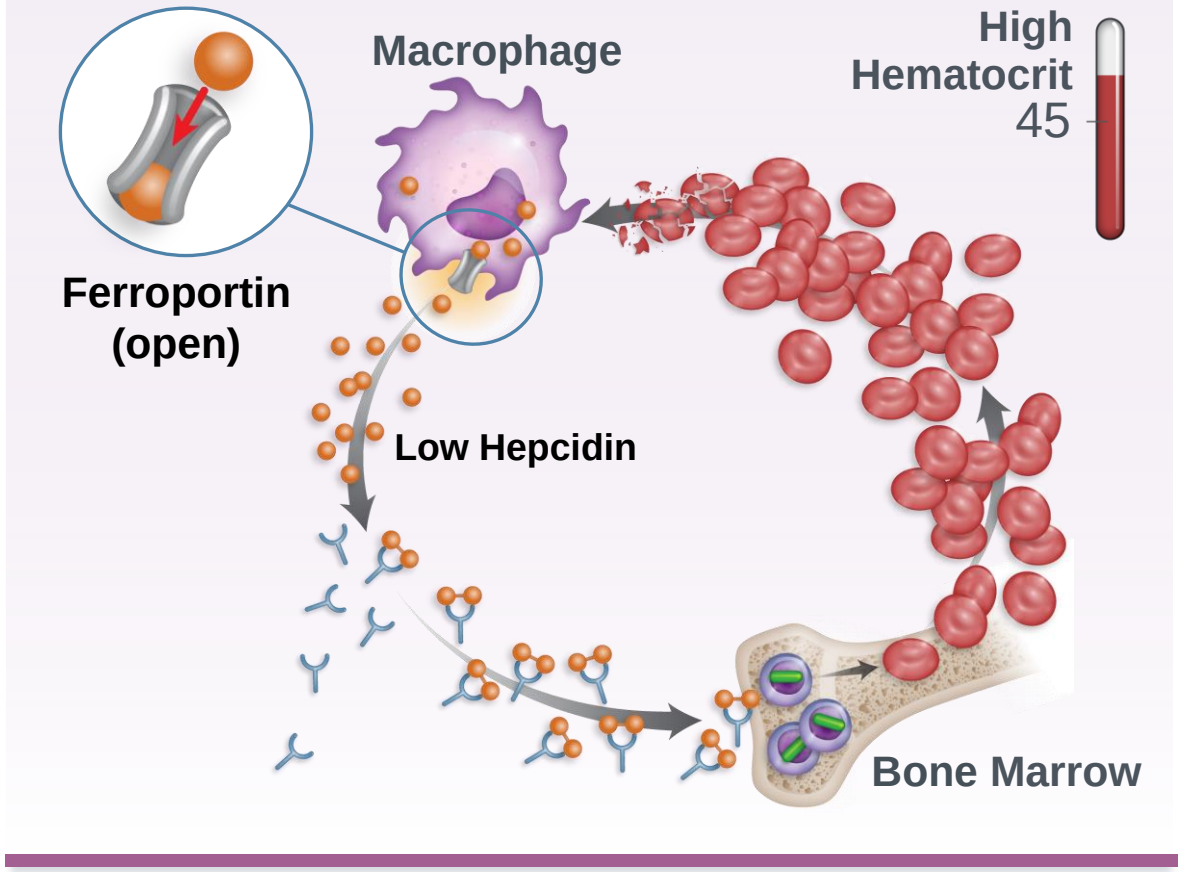
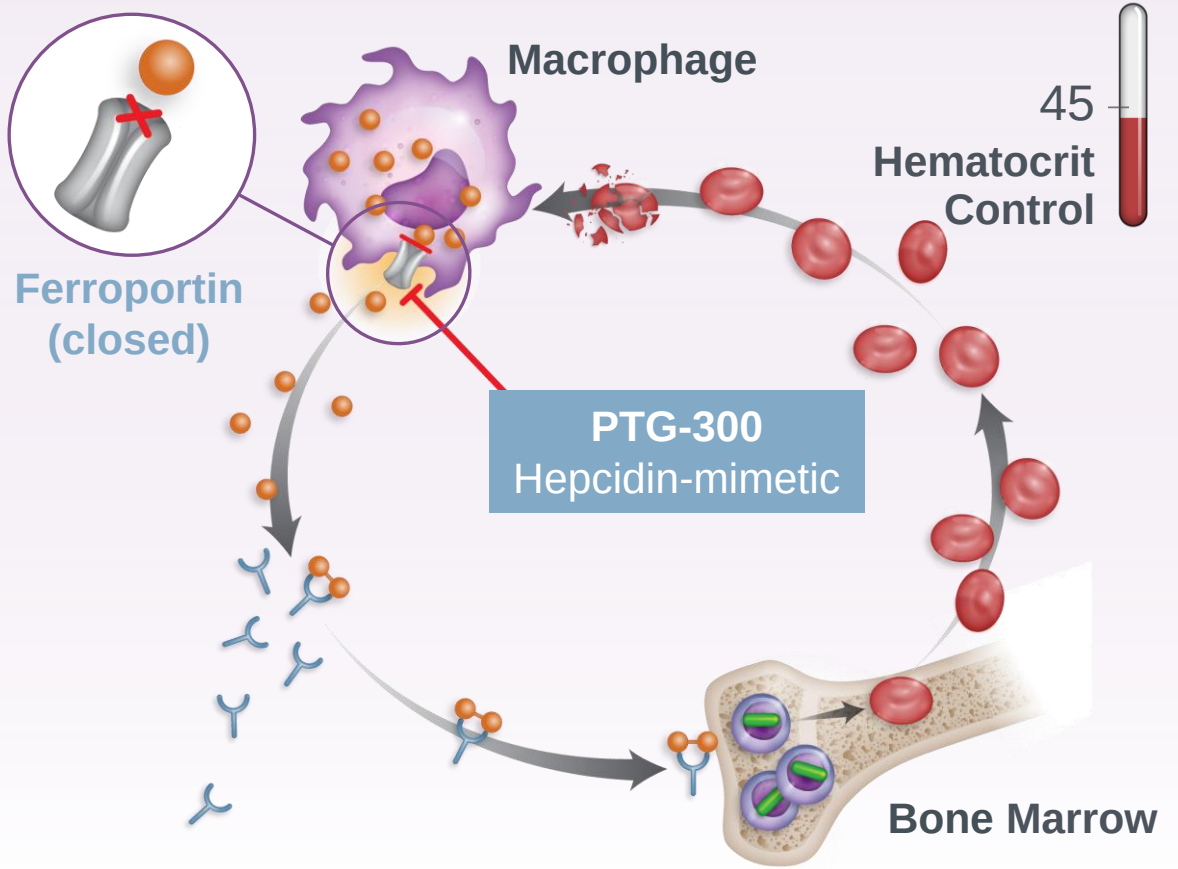
Rationale for using Hepcidin-Mimetics (PTG-300) in PV

Erythropoiesis in Polycythemia Vera



PTG-300 Suppresses PV Erythropoiesis



Transferrin (TF) · Iron (Fe) · TF-FE

Erythroblast · JAK2 · Red Blood Cell

Protagonist Therapeutics

Background

- Polycythemia vera (PV) is characterized by increased red blood cell production. Patients are treated with periodic therapeutic phlebotomy (TP) +/- cytoreductive therapy to maintain hematocrit levels <45%
- PV patients, however, likely spend significant time with hematocrit levels >45%, thereby potentially increasing their risk of thrombosis (Marchioli et al, NEJM 2013)
- The goal of TP is to generate iron deficiency which is thought to be needed to dampen PV erythropoiesis but it is thought to contribute to PV associated systemic symptoms due to the depletion of iron stores in non-hematopoietic tissues.
- **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.

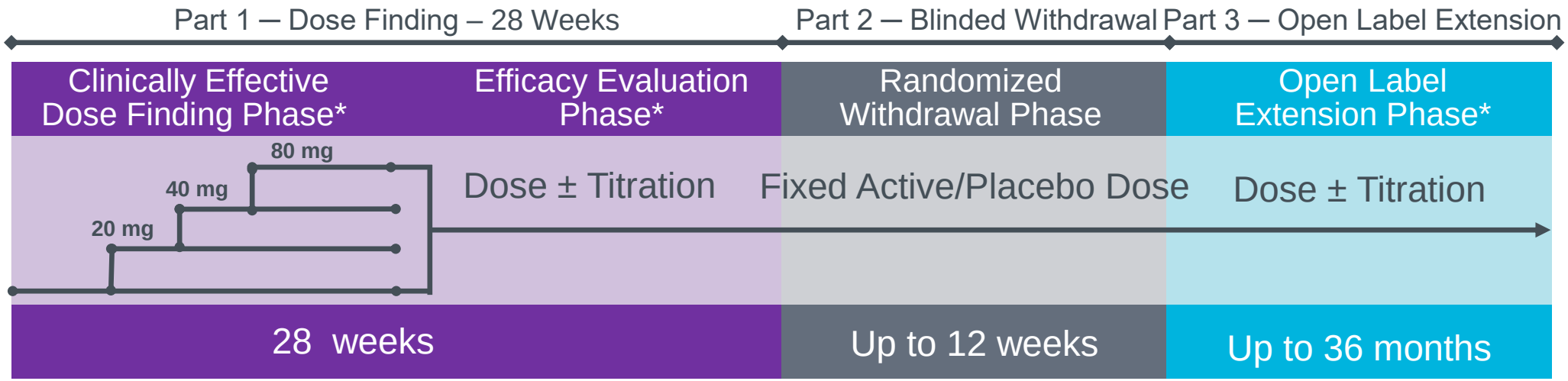
Phase 2 Trial of PTG-300 (Rusfertide) in 63 PV Patients

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 PTG-300 dose were phlebotomized to HCT < 45% to standardize the starting HCT
PTG-300 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%*

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

Baseline Characteristics of Study Participants

Characteristics (n = 63)	
AGE	
Range	27-76 years (Mean = 56.3 yrs)
GENDER	
Females	18 (28.8%)
Males	45 (71.4%)
RISK	
Low	28 (44.4%)
High	35 (55.6%) [Age based – 36.5%, Thrombotic events – 19.0%]
DURATION SINCE PV DIAGNOSIS	
<1 yr	12 (19.0%)
1 - <3 yrs	23 (36.5%)
3 - <5 yrs	9 (14.3%)
≥5 yrs	19 (30.2%)

Characteristics (n = 63)	
THERAPIES	
PHL only	31 (49.2%)
PHL + HU	18 (28.6%)
PHL + IFN	8 (12.7%)
PHL + RUX	3 (4.8%)
PHL +Multiple Agents	3 (4.8%)
NUMBER OF PHL IN 28 WEEKS PRIOR	
2-3	15 (23.8%)
4-5	33 (52.3%)
≥6	15 (23.8%)
Range	2-10 (Mean 4.71)
DAYS BETWEEN PHLEBOTOMIES	
Median	35

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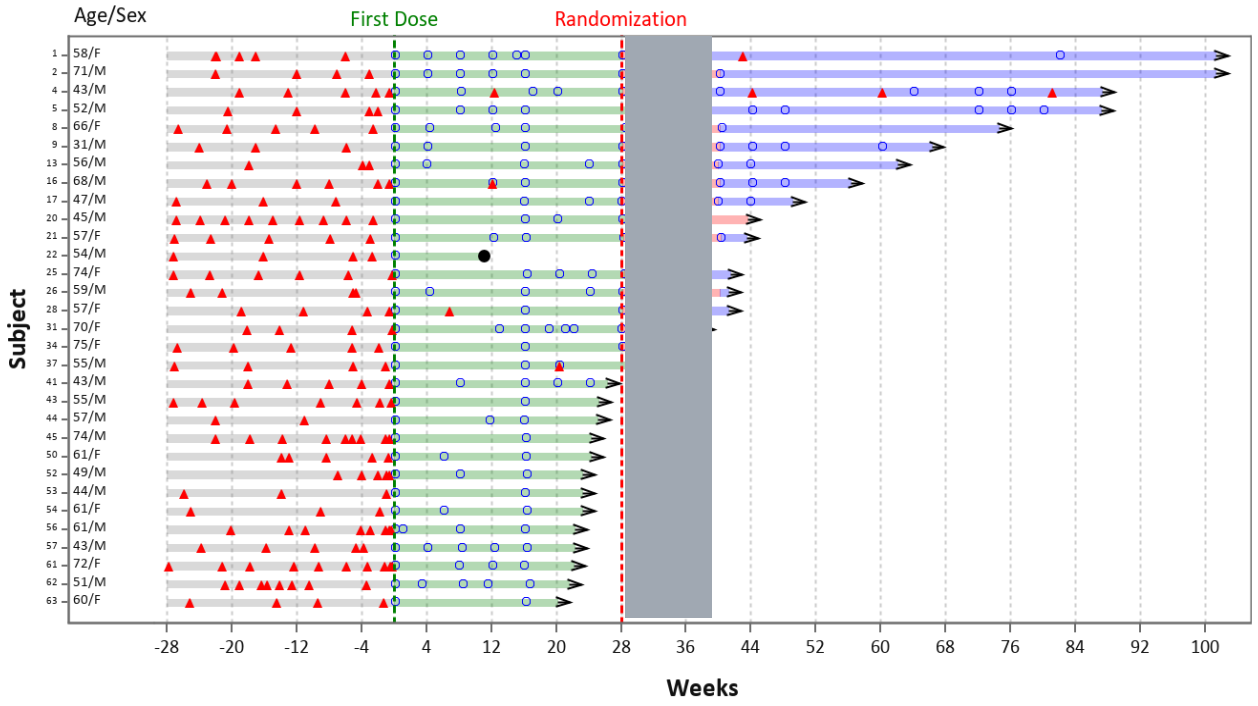
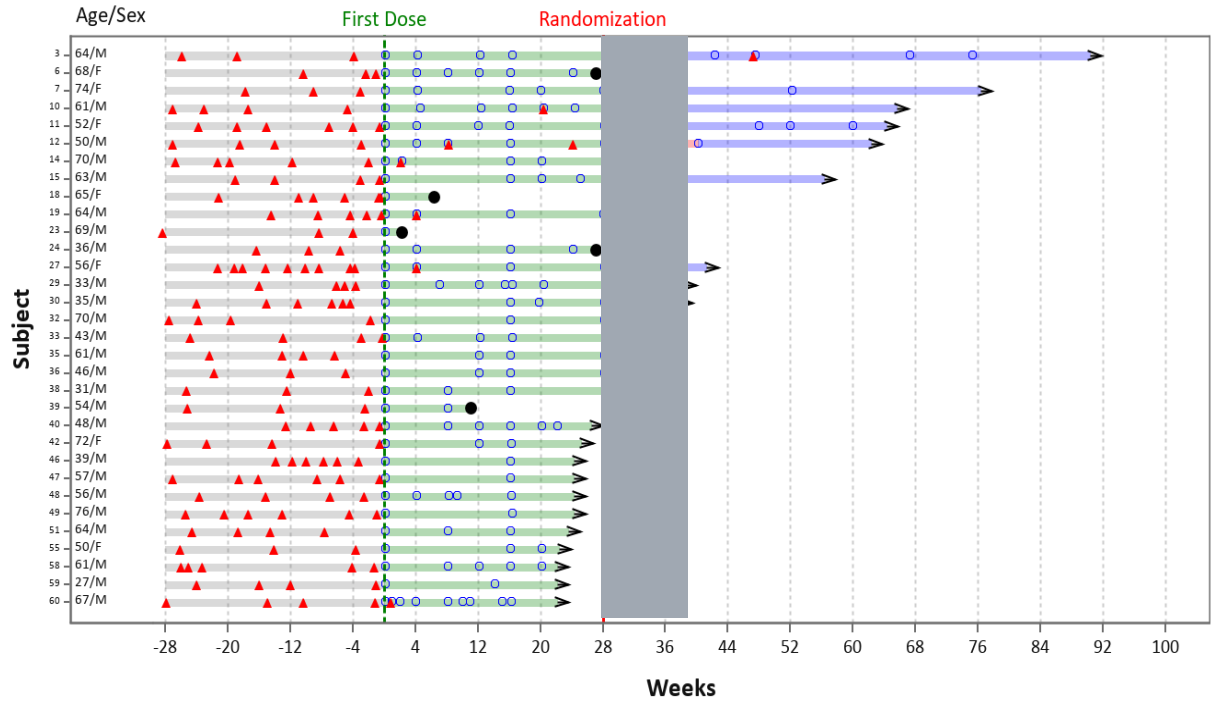
Effect of Rusfertide on Phlebotomy Frequency

PHLEBOTOMY ONLY (N=31, 49%)



PHLEBOTOMY + CYTOREDUCTIVE (N=32, 51%)



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

Median Dose 40-60 mg/week

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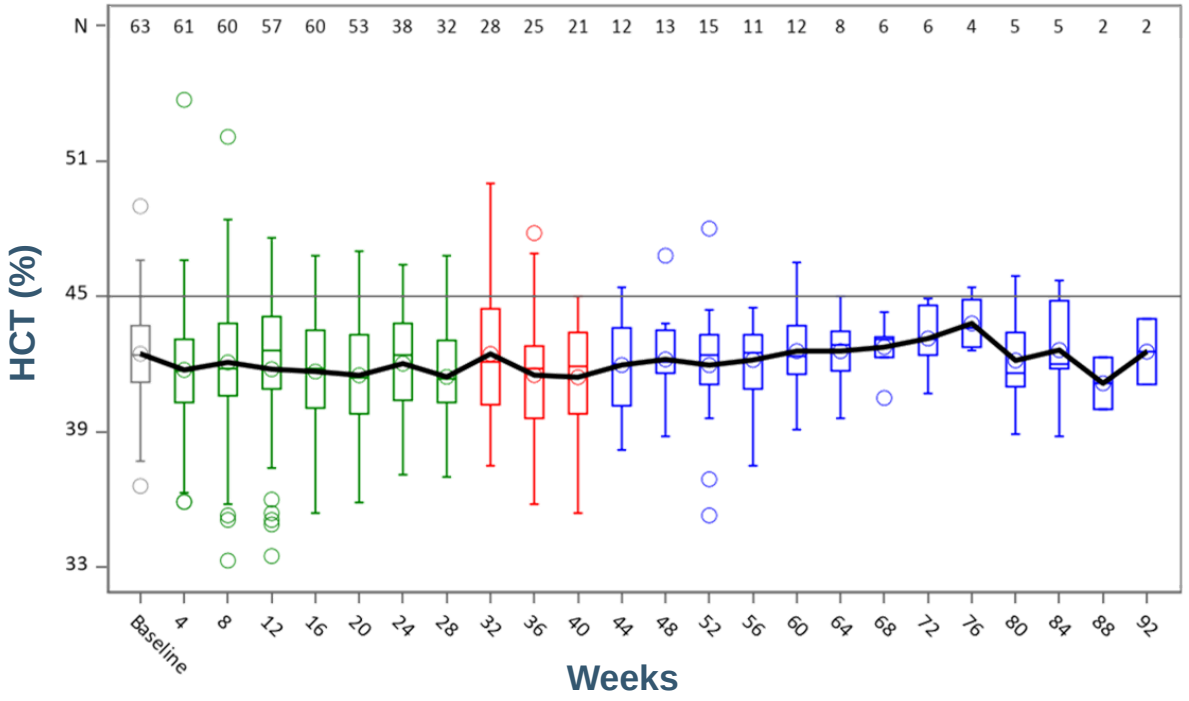
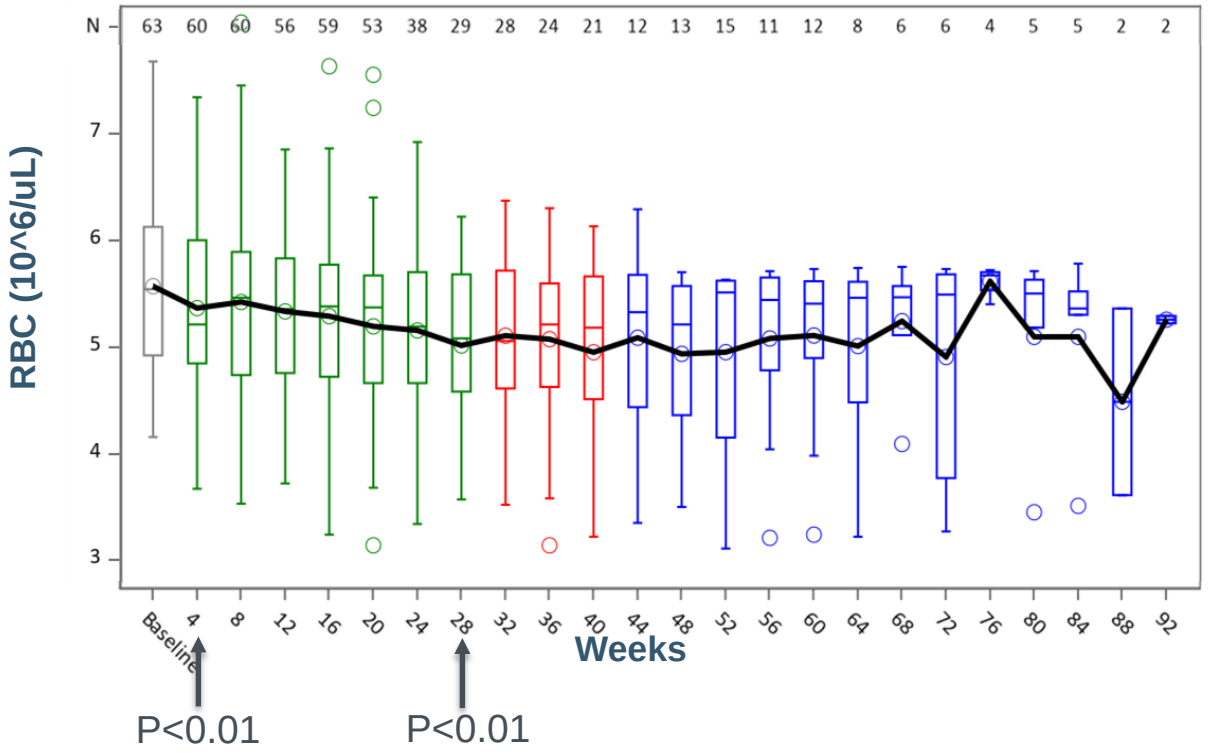
Rusfertide Controls HCT and Reduces RBC Count

Rusfertide Controls HCT for 1.5 year



Rusfertide reduces RBC Count in PV patients



Screening | Part 1 – Dose Finding | Part 2/3 – Blinded Withdrawal/OLE | Part 3 – Open Label Extension

AVAL = Raw Value
Box whiskers extend up to 1.5 times interquartile range.

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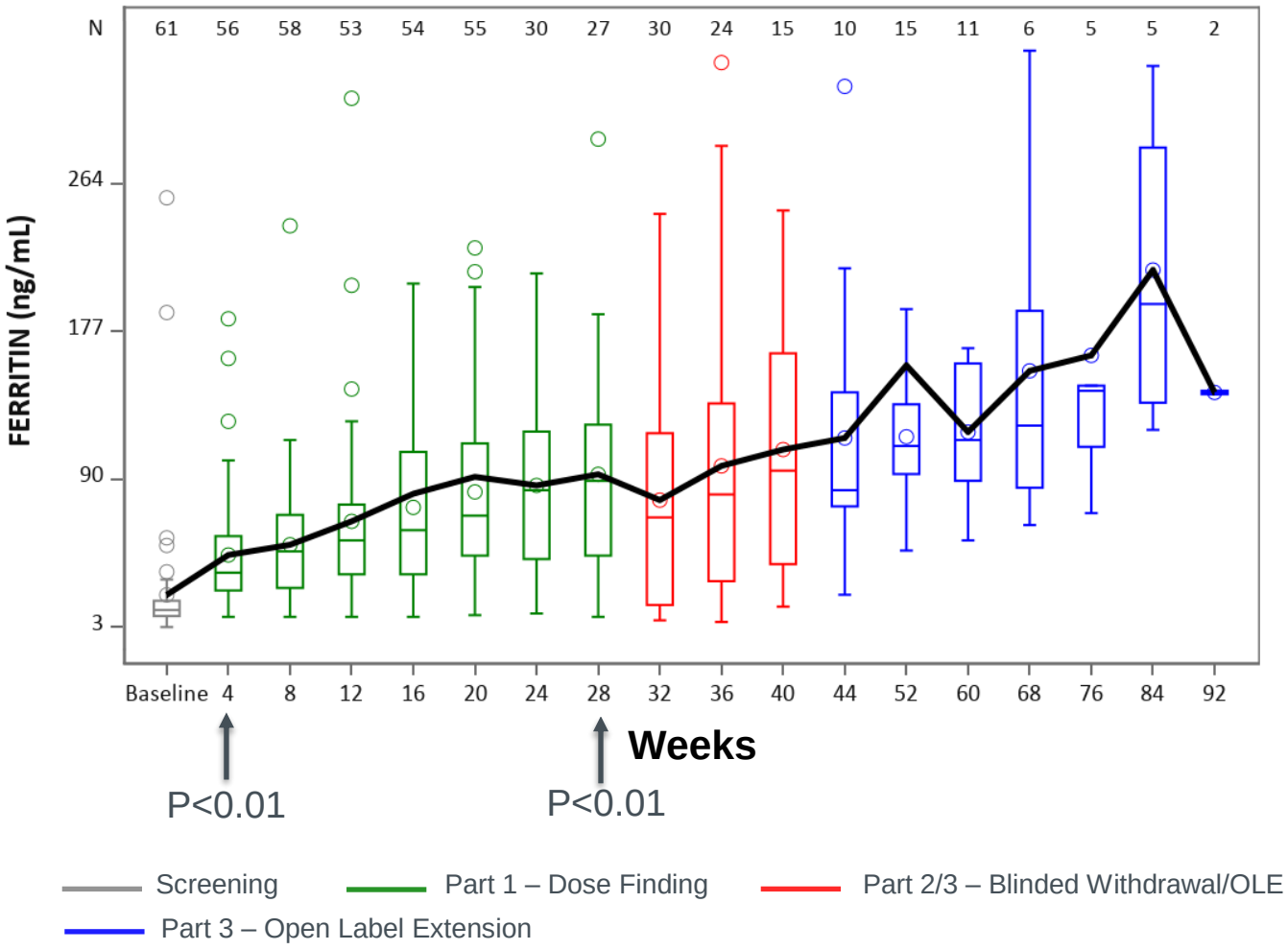
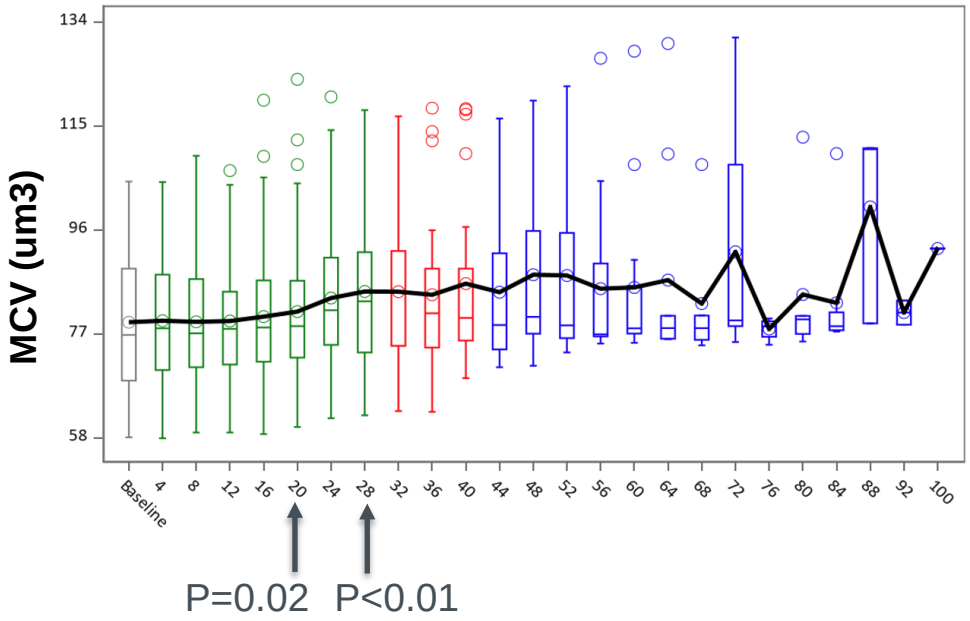
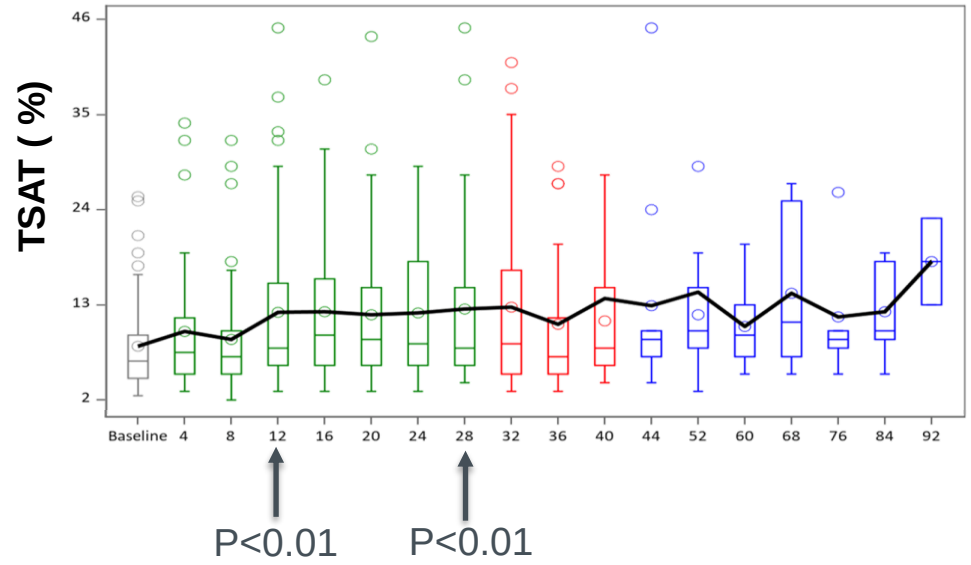
Rusfertide Normalizes Iron Stores







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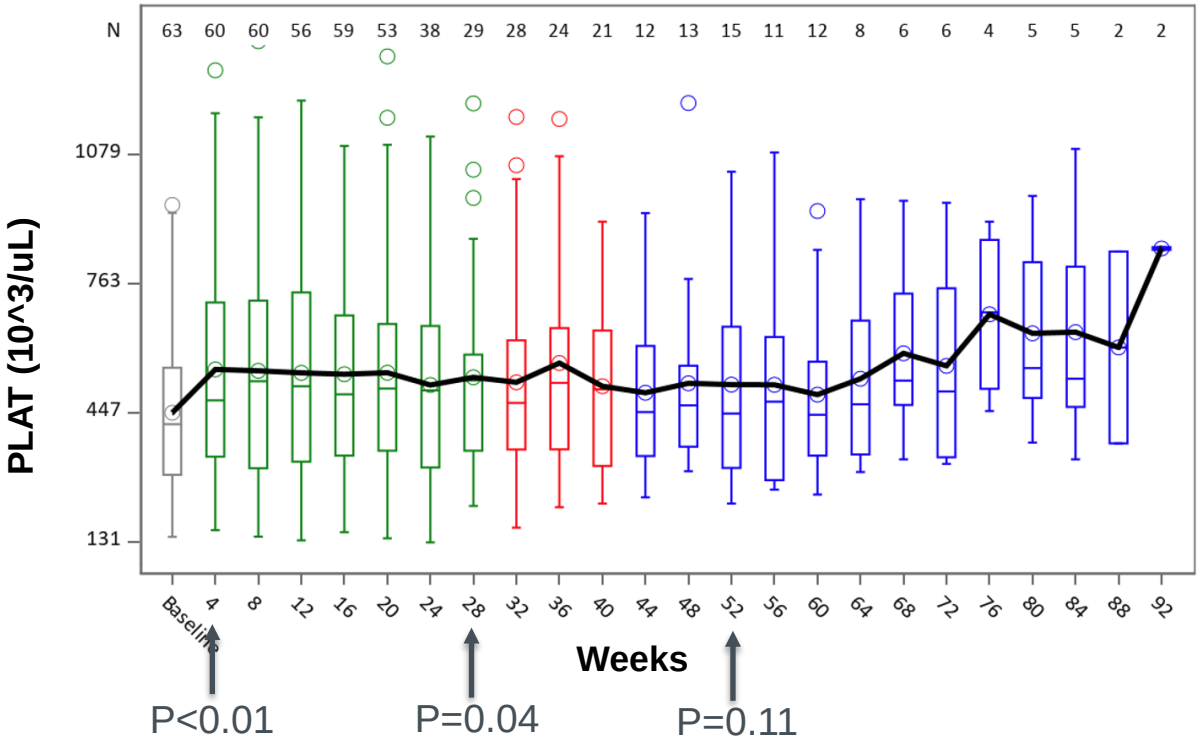
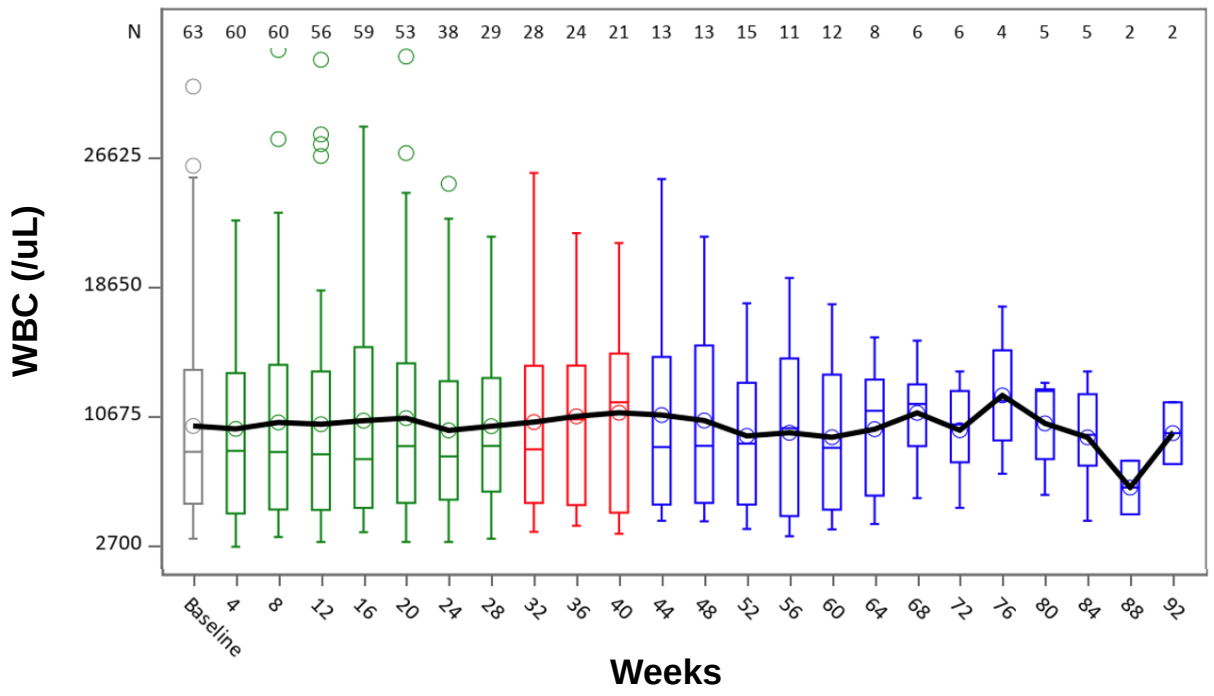
Effects of Rusfertide on Platelet and WBC Counts

Platelets



WBC



Screening | Part 1 – Dose Finding | Part 2 – Blinded Withdrawal | Part 3 – Open Label Extension

AVAL = Raw Value
Box whiskers extend up to 1.5 times interquartile range.

All increases in Platelet numbers < 20%

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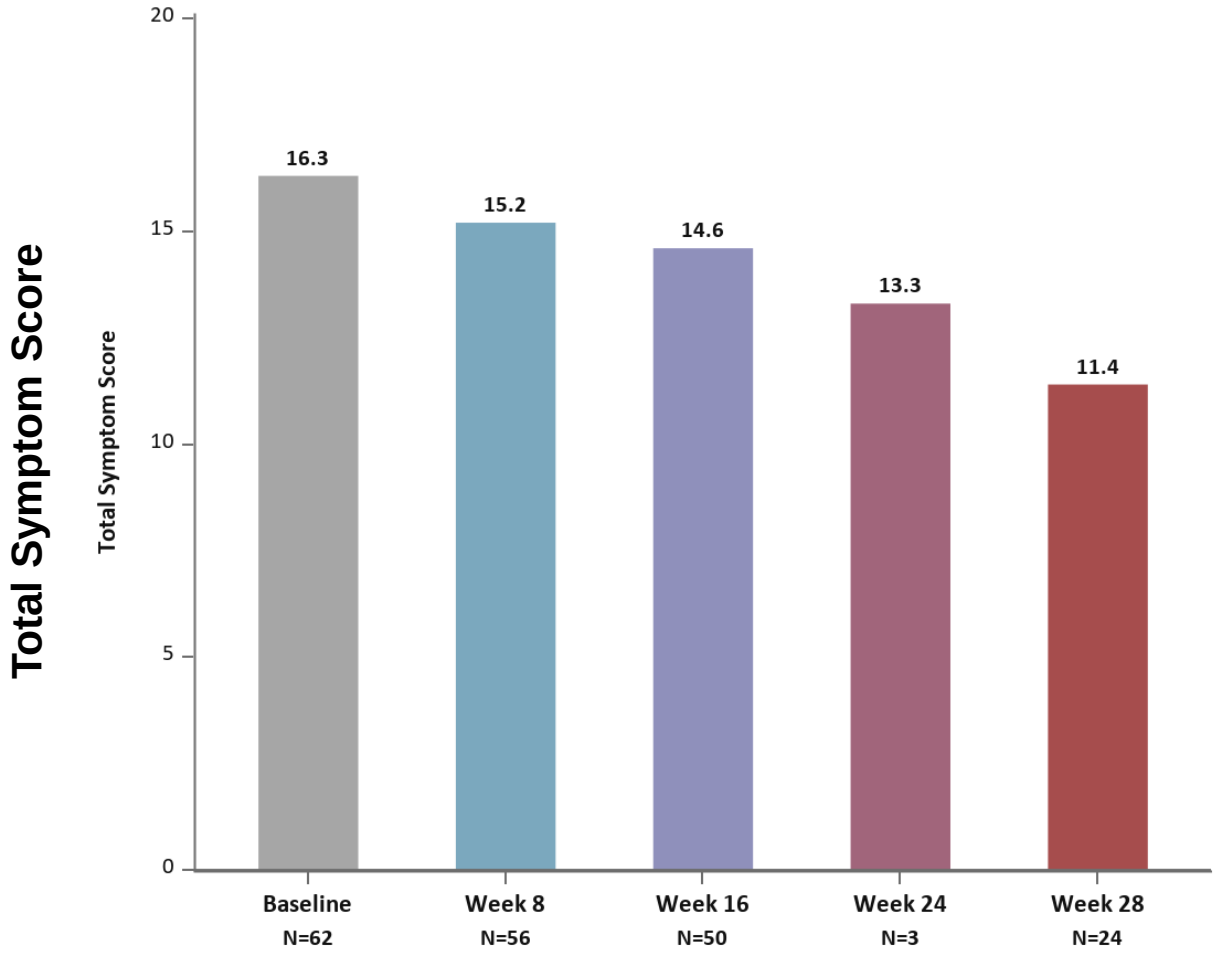
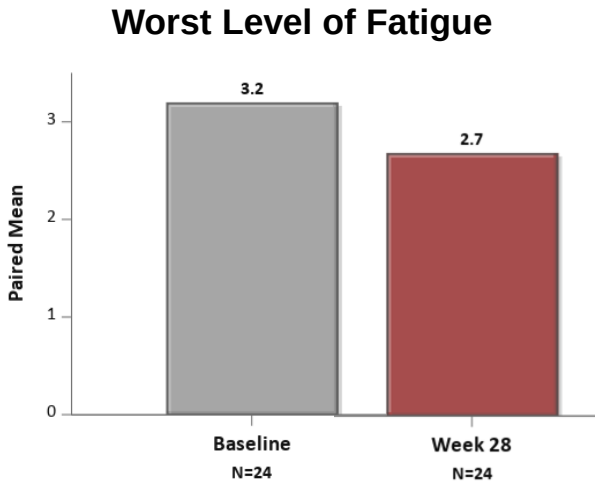
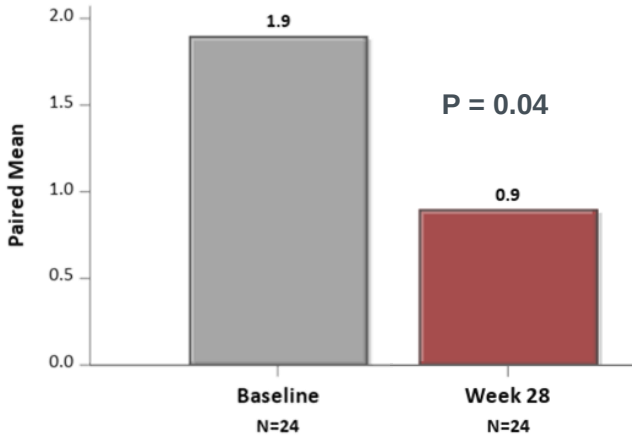
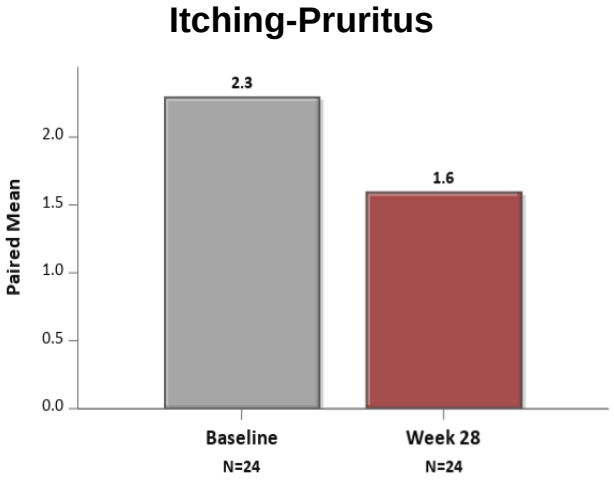
Improvement in MPN-TSS Scores Following Rusfertide









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Adverse Events Experienced on Rusfertide

System Organ Class. - Preferred term	AE n (%)
Total number of Subjects	***63***
No. of subjects with treatment-emergent AE	***55 (87)***
Blood and Lymphatic Disorders	12 (19.0)
Anemia	9 (14.3)
Gastrointestinal disorders	20 (31.7)
Nausea	8 (12.7)
Infections and infestations	11 (17.5)
Metabolism and nutrition disorders	9 (14.3)
Musculoskeletal and connective tissue disorders	27 (42.9)
Nervous system disorders	21 (33.3)
Psychiatric disorders	7 (11.1)
Insomnia	4 (6.3)
Renal and urinary disorders	5 (7.9)
Respiratory	14 (22.2)
Skin and subcutaneous tissue disorders	23 (36.5)
Pruritis	9 (14.3)

- **Most Drug related AEs were Grade 1 or 2**
- No Grade 4 or 5 Events
- **SAE's** Syncope, peripheral artery aneurism, gastroenteritis, chest pain, AML, squamous cell carcinoma (skin), melanoma & basal cell carcinoma
- Injection site reaction (ISRs) were most common and associated with 28.1% of injections. All ISRs were transient, and no patient discontinued due to ISR.
- One subject stopped treatment due to AE within 2 weeks (asymptomatic thrombocytosis)
- No clinically significant laboratory abnormalities.
- No Anti Drug Antibody response was noted in any patient

FDA Clinical Hold in Sept, 2021 Was Lifted after 3 Weeks

- Potential of carcinogenicity was evaluated in a GLP Carcinogenicity Study, RasH2 Mice, 2 instances of malignant squamous cell carcinoma were observed (1 male + 1 female mouse; not statistically significant).
- **FDA initially considered events Rusfertide-related since they utilized combined endpoint of benign squamous cell papillomas and squamous cell carcinomas.**

Sex	Rusfertide							
	Male				Female			
Dose Level (mg/kg/dose)	0	6.25	12.5	25	0	6.25	12.5	25
Number of Animals	25	25	25	25	25	25	25	25
Skin/Subcutis								
B-Papilloma, squamous cell	0	2	2	2	0	0	3*	3*
M-Carcinoma, squamous cell	0	1	0	0	0	0	1	0
B-Papilloma, squamous cell or M-Carcinoma, squamous cell	0	3*	2	2	0	0	4*	3*

B = Benign; M = Malignant. * = $p<0.05$

- **The clinical hold was lifted after 3 weeks.**
- No Rusfertide-related neoplastic lesion findings have been noted in other preclinical toxicity studies including 6-month rat and 9-month cynomolgus monkey chronic toxicity studies.
- A 2-yr rat carcinogenicity GLP study is ongoing and a dose finding rat study has been completed.

Reported Cases of Cancer in PV Subjects on Rusfertide

Subject	Condition/Trial	Prior medical condition/treatment Rx	Event	Rusfertide Exposure @ Event	Report date	Subject Disposition	Relationship to Rusfertide by PTGX (Initial*/Post-rasH2 Findings)
73 yrs. Female	Polycythemia Vera PTG-300-04	Basal cell carcinomas Melanoma Squamous cell carcinomas (SCC)-14 in 2yrs prior to enrollment.	3 SCC in situ; rx: curettage 3 SCC in situ; rx: Moh's	49 days 85 days	Q3 2021	Continued through 10/21	Not related/Possibly related
65 yrs. male	Polycythemia Vera PTG-300-04	Hydroxyurea (6 years) Thyroid cancer treated with iodine 131	MPN Blast Phase	9 months	Q3 2021	Discontinued	Not related/Possibly related

**Investigator viewed as not related*

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Conclusions

- **In phlebotomy dependent polycythemia vera (PV) patients 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 demonstrated similar efficacy in all categories of patients, independent of the PV patient risk category or concurrent therapy with hydroxyurea, interferon or ruxolitinib.
  - Rusfertide treated PV patients demonstrated a modest increase in platelet counts during the early phase of the trial(<20%). Study participation was halted in 1 patient due to asymptomatic thrombocytosis. In second patient with intractable headaches presumably related to the thrombocytosis Rusfertide therapy was continued and hydroxyurea therapy lead to symptomatic relief .
  - 1 patient developed MPN blast phase which was thought not to be related to Rusfertide.
- **Benefits from Rusfertide treatment was were noted in patient reported outcomes as assessed by MPN-SAF Total Symptom Score**
  - Attributed largely to the MPN-SAF sub-scores of fatigue and concentration (Brain Fog)
  - Consistent with improvement in total body iron stores as assessed by serum ferritin levels and increasing MCV & MCH.
- **The current results indicate that Rusfertide is safe and well tolerated:**
  - Most common AEs are transient injection site reactions
  - Most AEs were grade 1 or 2
- **After a 3-week clinical hold the Phase 2 Trial has resumed**
- **Enrollment in Phase 3 trial of Rusfertide will begin in Q1, 2022.**

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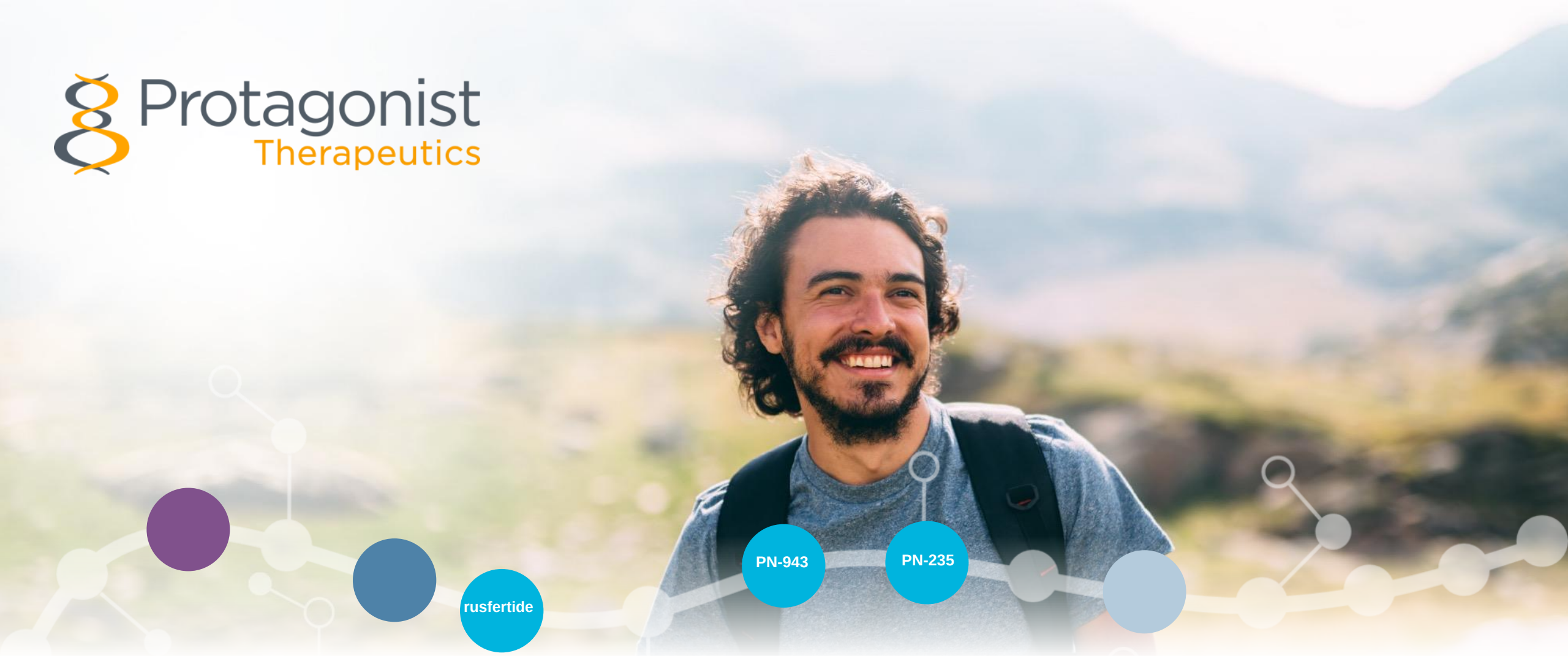
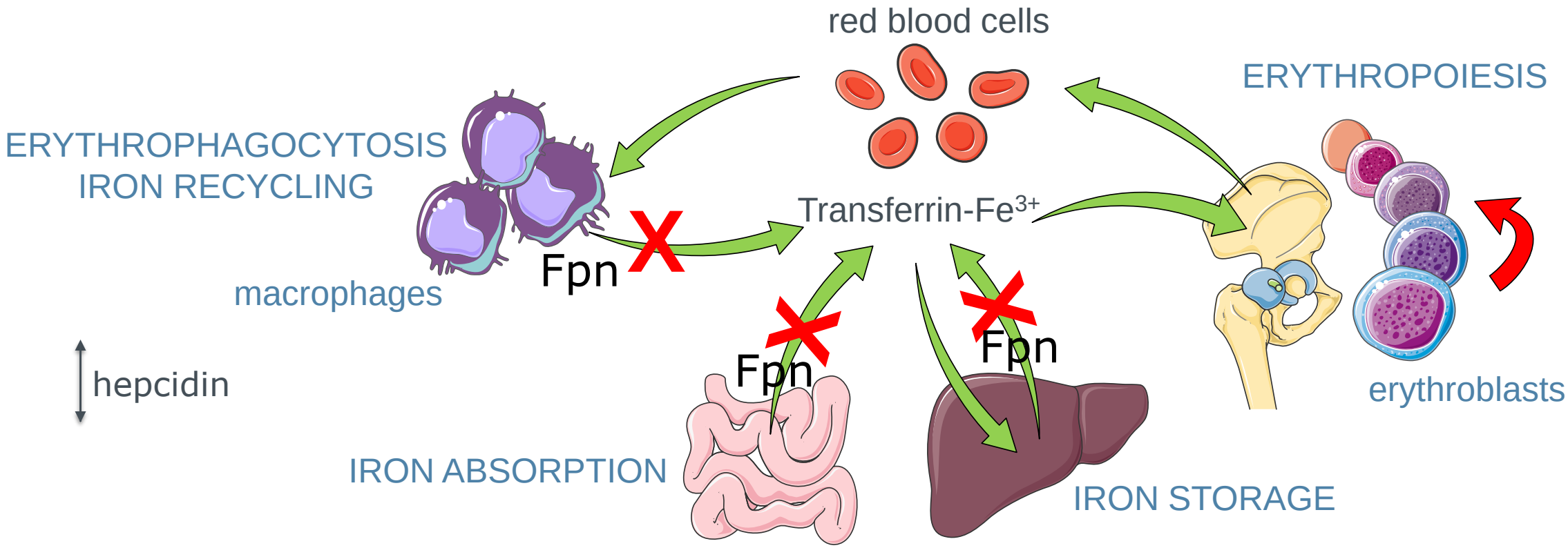


Oral Presentation 2

Rusfertide (PTG-300) Induction Therapy Rapidly Achieves Hematocrit Control in Polycythemia Vera Patients without the Need for Therapeutic Phlebotomy

Crosstalk between iron metabolism and erythropoiesis



Increased hepcidin results in iron sequestration to decrease iron availability for erythropoiesis

Adapted from **Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics: Clinical Principles and Applications** (7th edition), Chapter 12, Ginzburg YZ, Finberg KE. *Iron Metabolism and Related Disorders*

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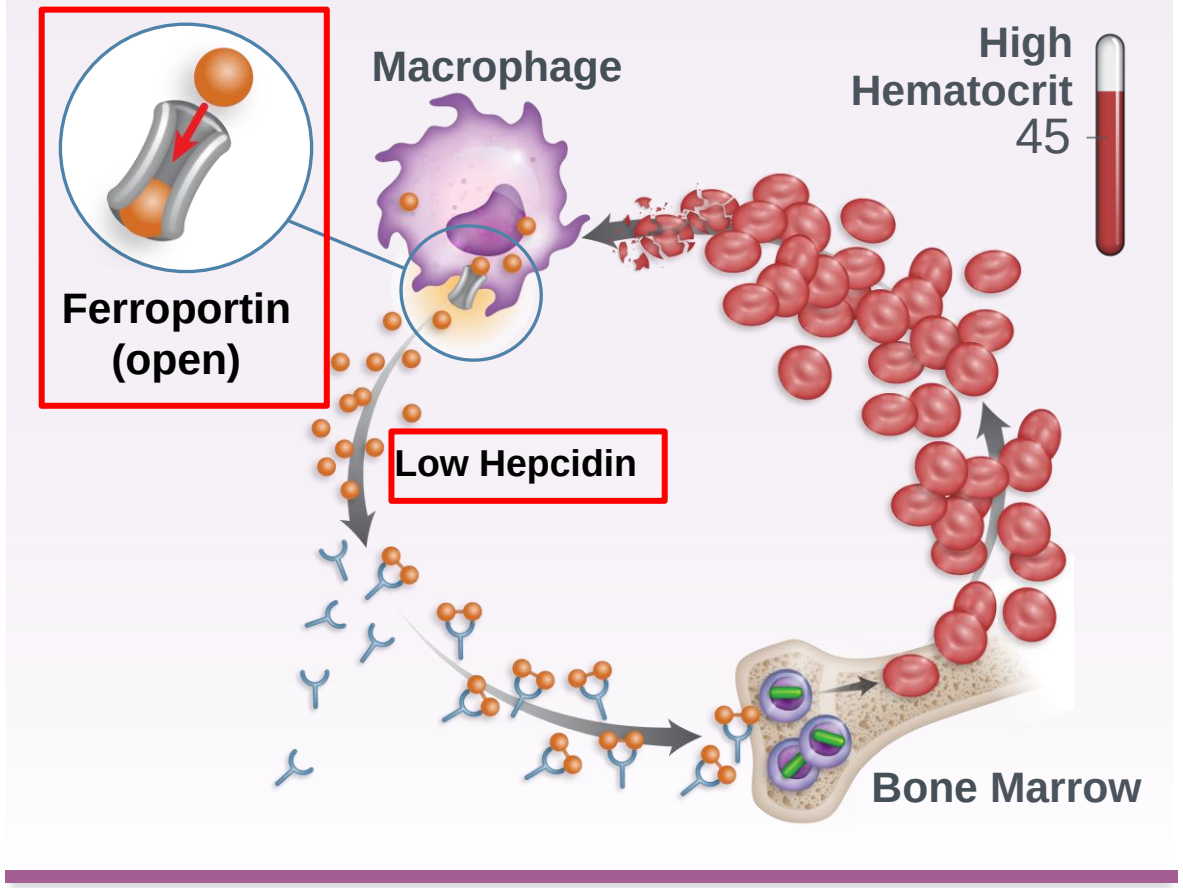
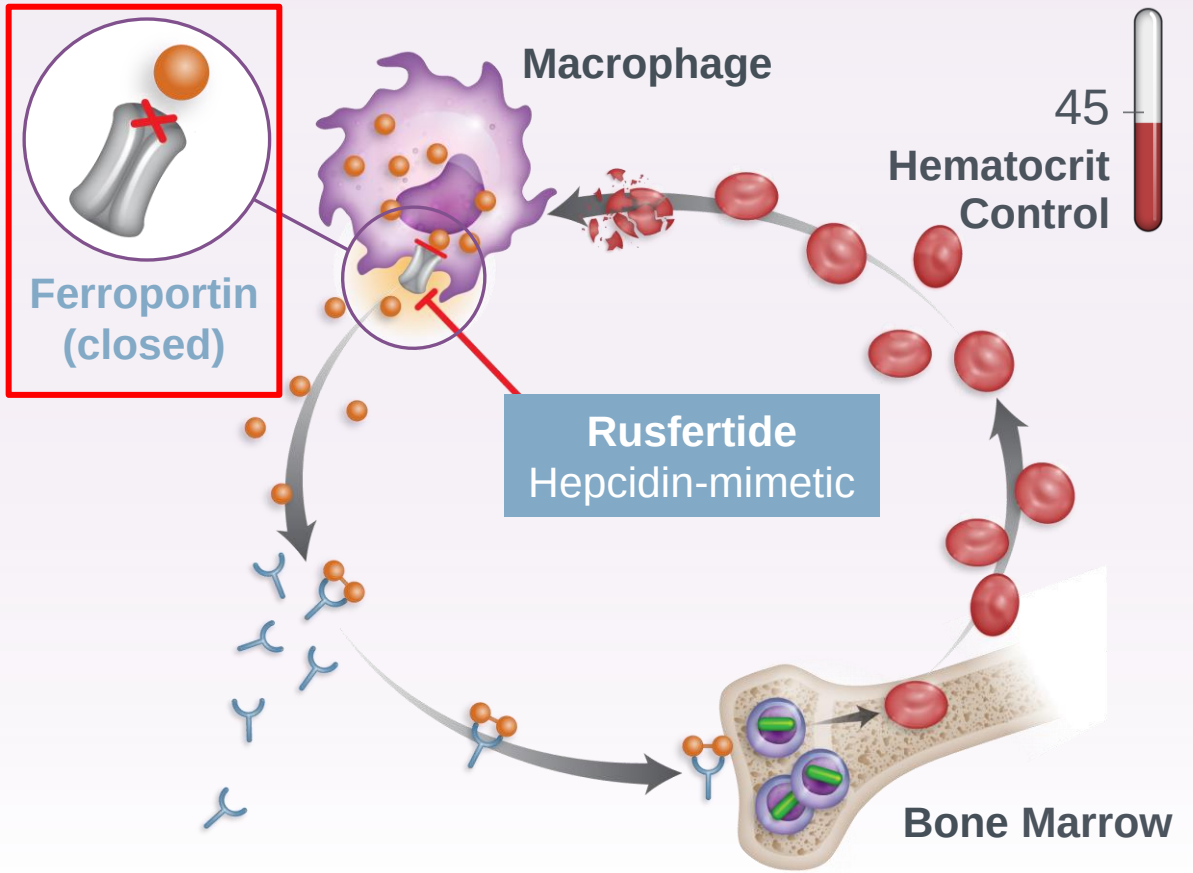
Rationale for using Hepcidin-Mimetics (PTG-300) in PV

Erythropoiesis in Polycythemia Vera



Rusfertide Suppresses PV Erythropoiesis



Transferrin (TF) · Iron (Fe) · TF-FE · Erythroblast · JAK2 · Red Blood Cell

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High Hematocrit Study (PTG-300-08): Overview of Study Design

- Patient met the WHO criteria for PV diagnosis;
- Baseline hematocrit (HCT) > 48%, and a history of ≥3 HCT values > 48% in the year prior to enrollment;
- High-risk and low-risk subjects treated with TP alone or with concurrent cytoreductive therapy were eligible;
- Rusfertide was added on to each subject's current therapy;
- Initial dose: 40 mg SQ twice weekly;
- Maintenance dose: Once each subject's HCT decreased (< 45%) for 2 consecutive visits, physicians' choice to adjust dosing regimen to maintain HCT < 45%.

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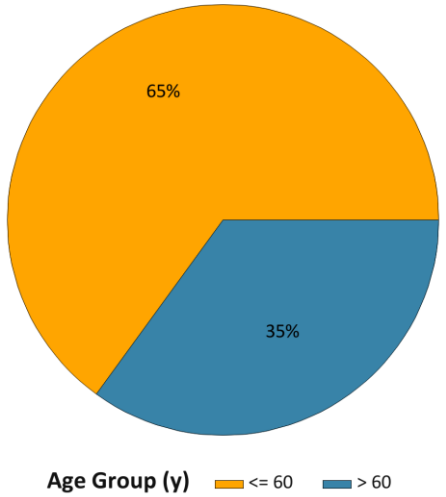
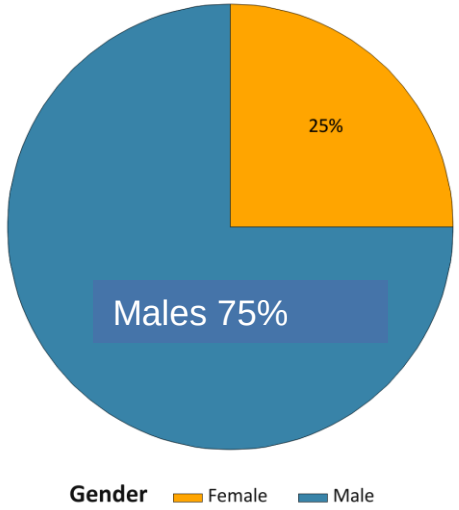
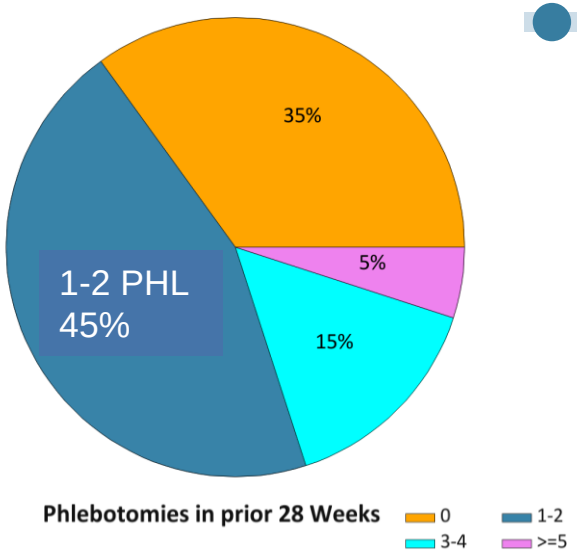
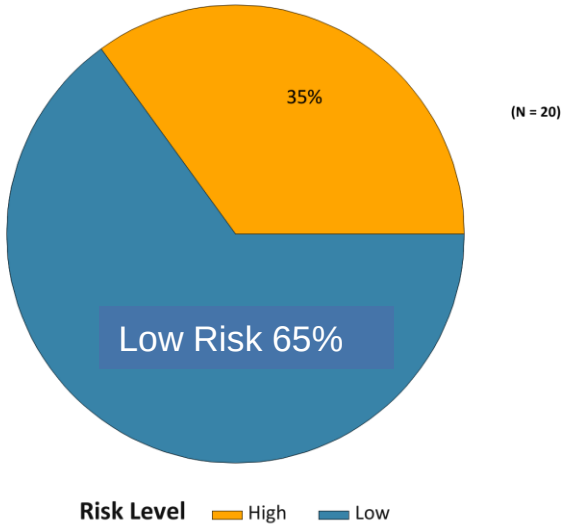
Full overview available at https://clinicaltrials.gov/ct2/show/NCT04767802

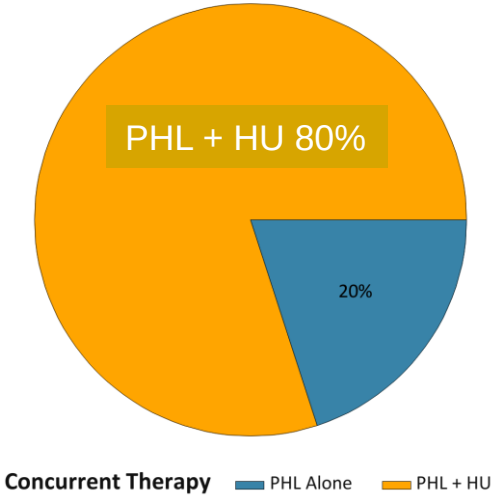
Baseline Characteristics of PV Subjects (n=20)

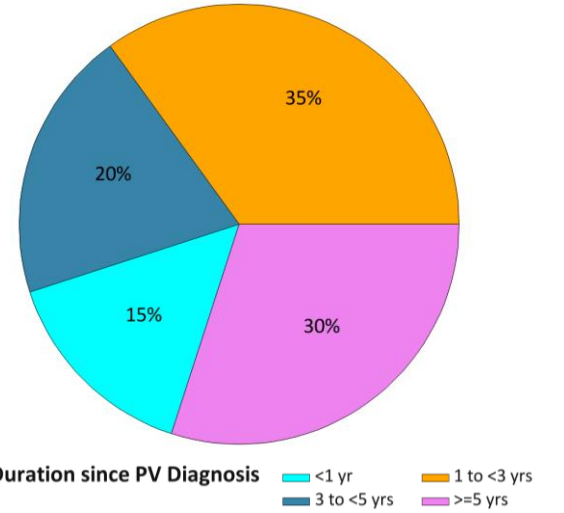








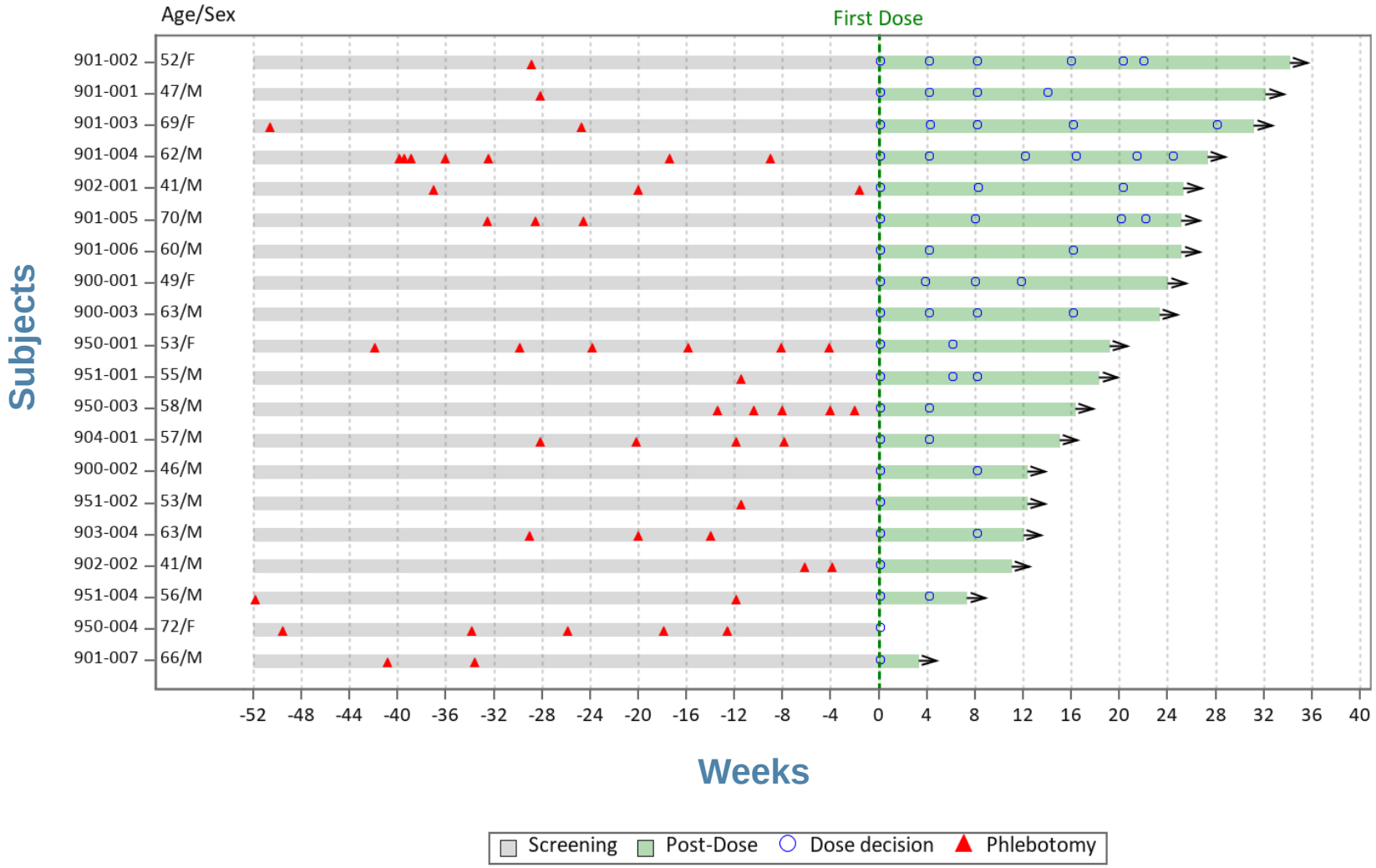




Protagonist Therapeutics

Data as of September 2021

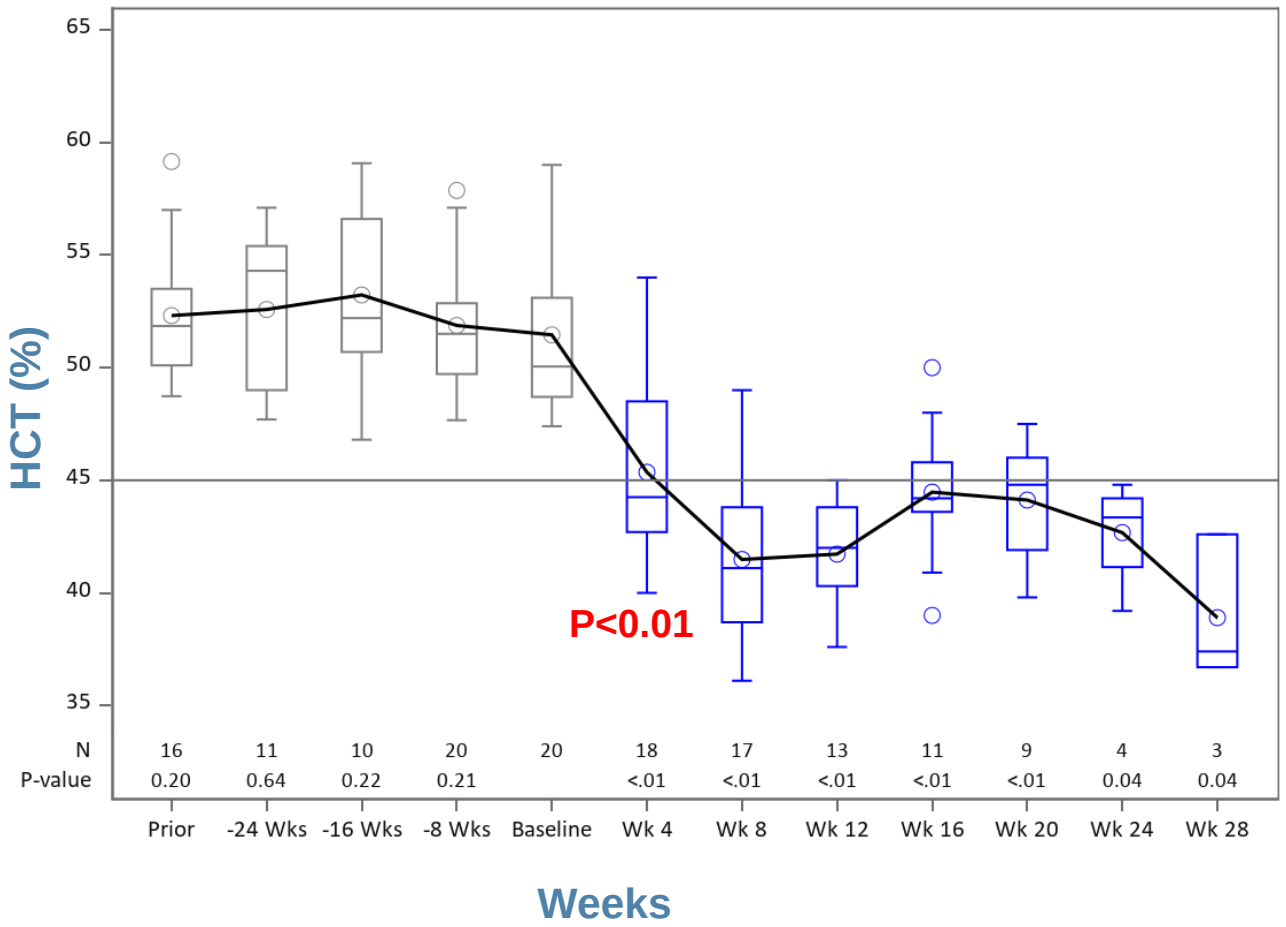
Therapeutic Phlebotomies Prior to and on Rusfertide



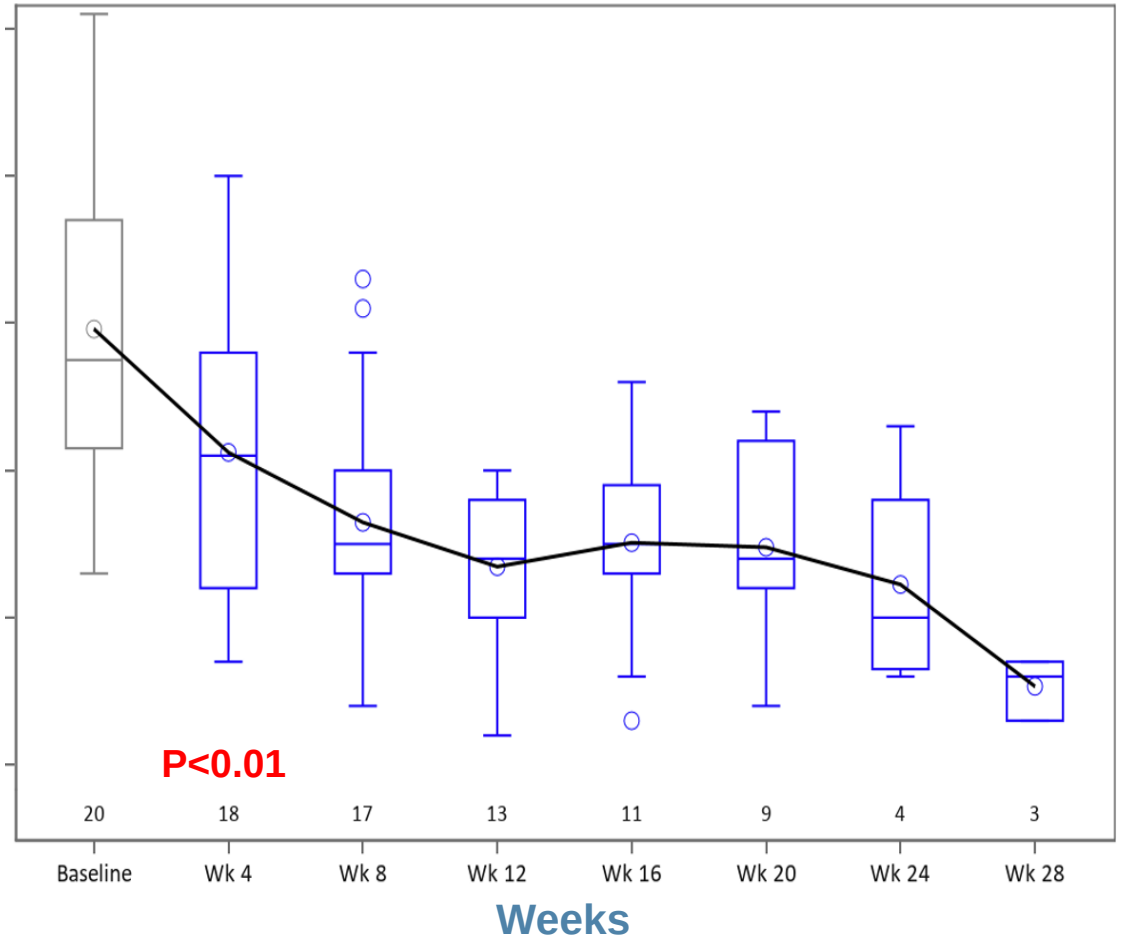
Protagonist Therapeutics

Rusfertide Rapidly Controls HCT and Reduces RBC

Rusfertide Immediately Controls HCT



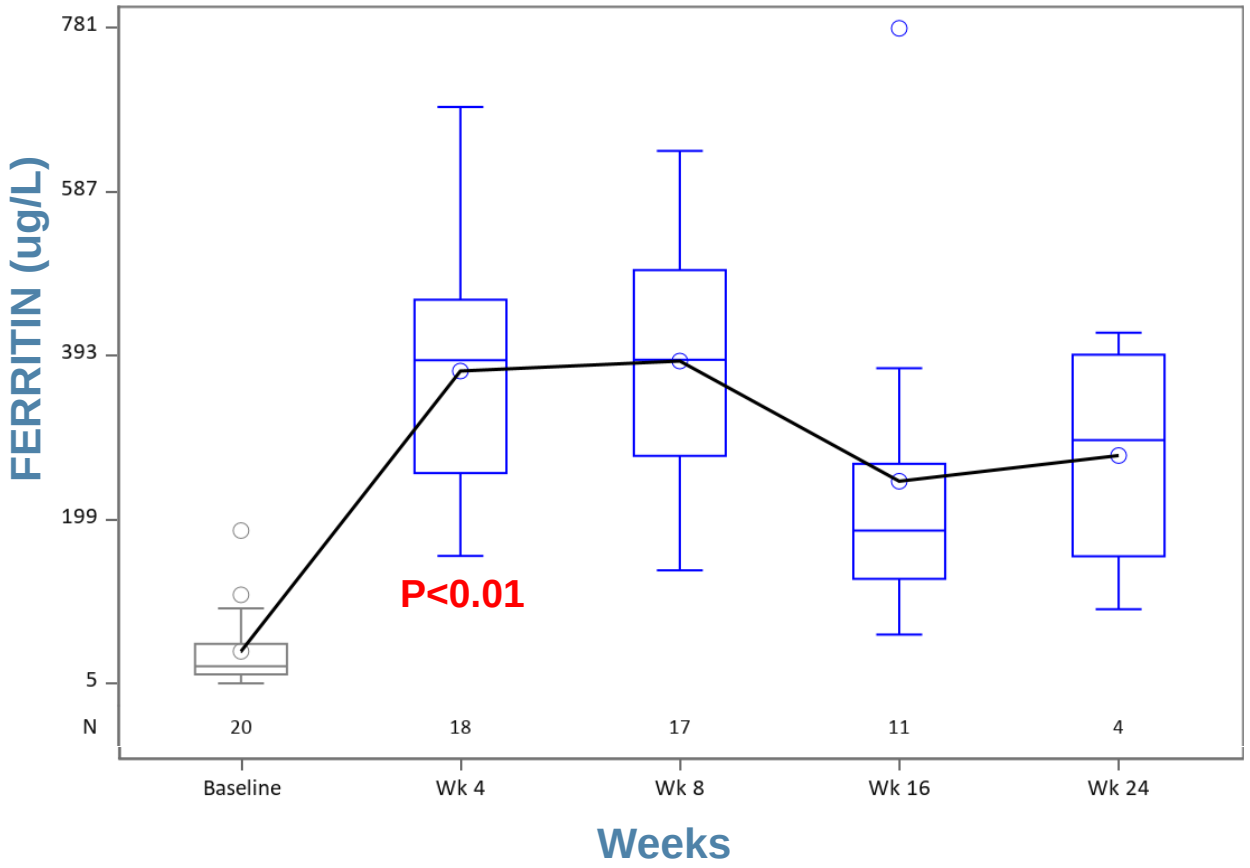
Rusfertide Immediately Reduces RBC Count

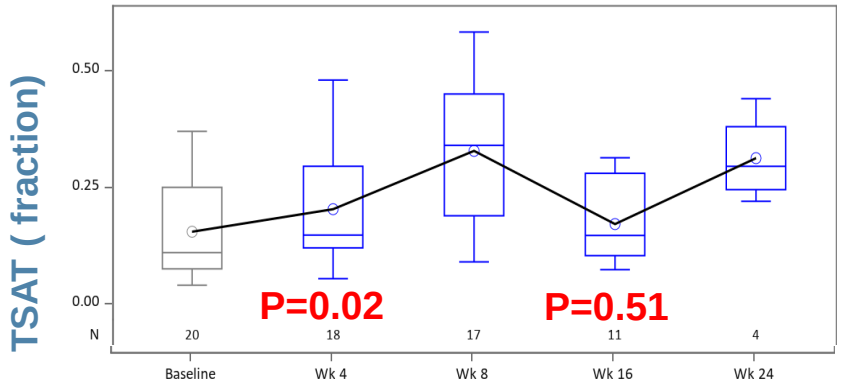


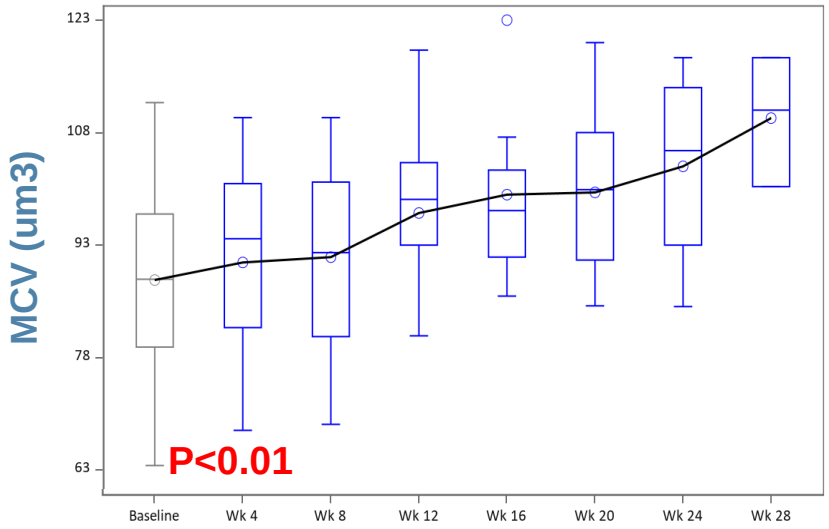
Screening PTG-300 MEAN

Protagonist Therapeutics

Rusfertide Normalizes Iron Stores





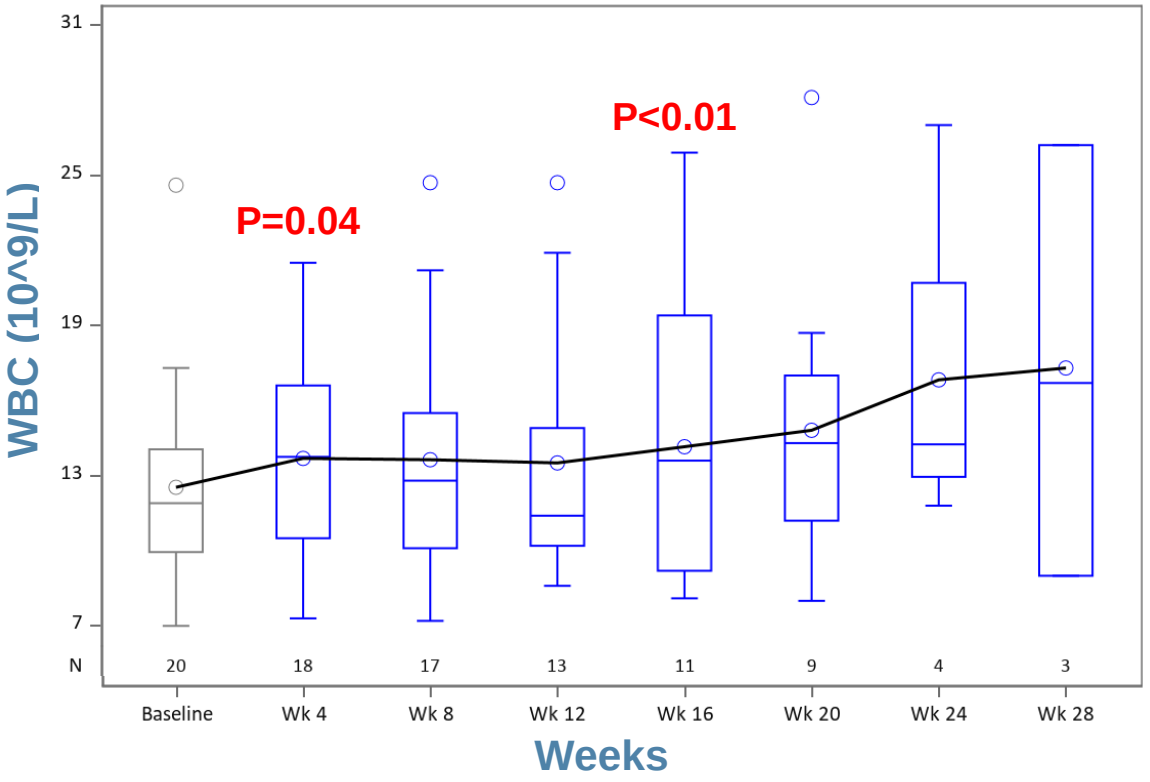


Screening PTG-300 MEAN

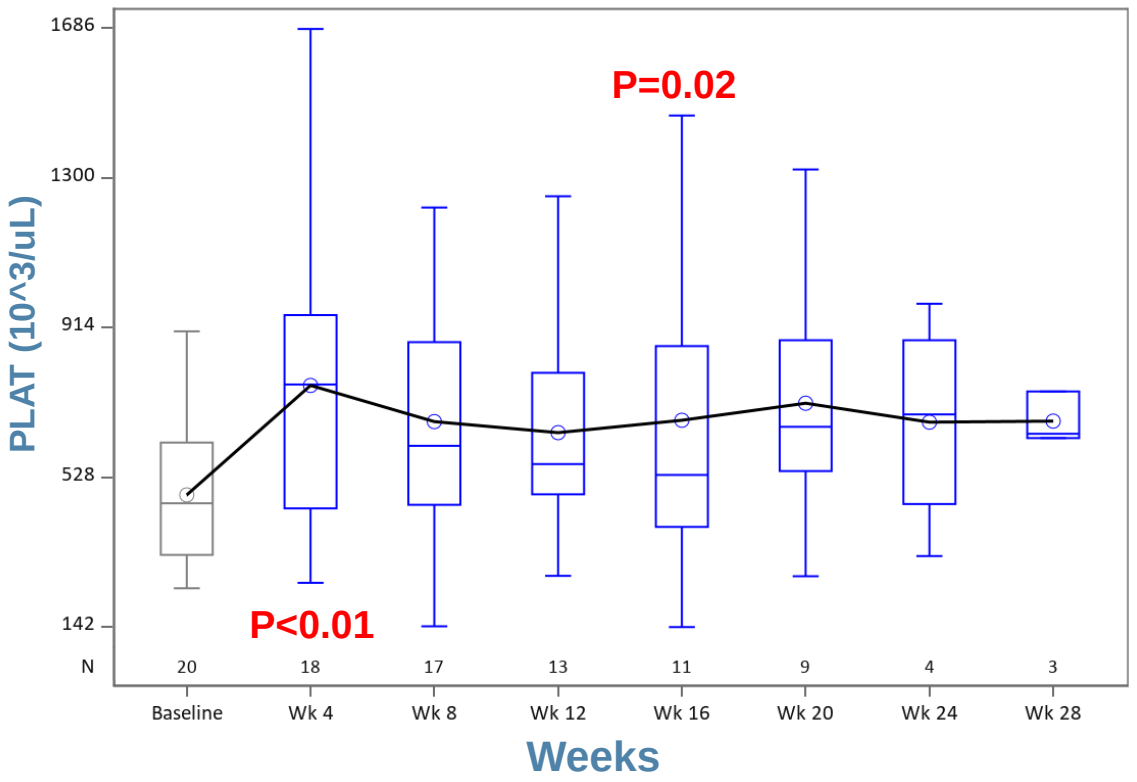
Protagonist Therapeutics

Effects of Rusfertide on Platelet Count and WBC Count

PTG-300 Leads to Increased WBC count



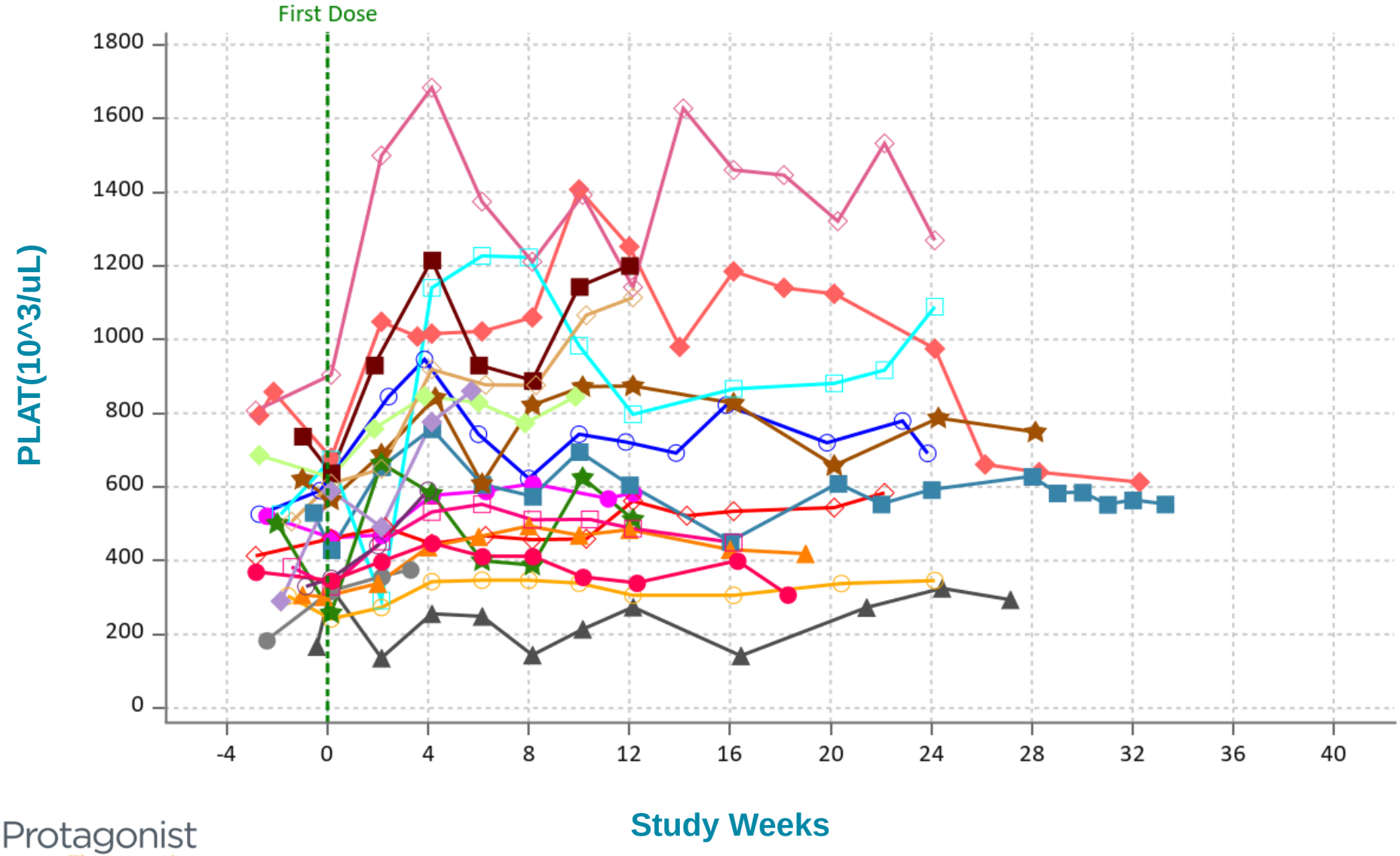
PTG-300 Leads to Increased Platelet Count



Screening PTG-300 MEAN

Protagonist Therapeutics

Platelets (10^3/uL) Over Time by Subjects



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Adverse Events in Ongoing Study PTG-300-08

System Organ Class Preferred term	All AEs n (%)
Total number of Subjects	***20***
No. of subjects with treatment-emergent AE	***13 (65.0)***
Blood and Lymphatic System	3 (15.0)
Thrombocytosis	3 (15.0)
Gastrointestinal disorders	3 (15.0)
Nausea	5 (8.1)
Musculoskeletal and connective tissue disorders	3 (15.0)
Nervous system disorders	5 (25.0)
Renal and urinary disorders	2 (3.2)
Skin and subcutaneous tissue disorders	4 (20.0)

- **Most Drug related AEs were Grade 1 or 2**
- One subject stopped treatment due to AE (Thrombocytosis without bleeding or thrombosis; Grade 4 according to investigator)
- Injection site reaction (ISRs) were most common and associated with 68% of injections. All ISRs were transient, and no patient discontinued due to ISR.
- No anti-drug antibody response was noted in any patient

Conclusions

- PTG-300 (Rusfertide) induction therapy with twice weekly dosing is effective at rapidly achieving target hematocrit below 45% without phlebotomy in all erythrocytotic PV patients.
- PV patients initially on twice weekly injections of Rusfertide rapidly lower hematocrit levels enabling successful transition to and maintenance on weekly Rusfertide treatment.
- The clinical significance of increased platelet and WBC counts (in the absence of a thrombotic event) in a subset of PV patients on Rusferitide remains to be fully evaluated with longer follow up of a larger cohort of PV patients.
- Taken together, use of Rusfertide in erythrocytotic PV patients represents a novel therapeutic direction for patients unwilling or unable to utilize the current standard of care.

Poster Presentation 1

A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera

A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera

Srdan Verstovsek, MD PhD[1] , Andrew Kuykendall, MD[2] , Ronald Hoffman, MD[3] , Yelena Ginzburg MD[3], Naveen Pemmaraju MD[1], Frank Valone MD[4], Nishit Modi PhD[4], Sarita Khanna PhD[4], Paula O'Connor MD[4], Suneel K Gupta PhD[4], Jean-Jacques Kiladjian MD, PhD[5]

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Protagonist Therapeutics

Disclosures

Verstovsek: *Novartis:* Consultancy and Research Funding; *Abbvie:* Research Funding; *AstraZeneca:* Research Funding; *Blueprint Medicines:* Research Funding; *Bristol Myers Squibb:* Research Funding; *Celgene:* Consultancy, Research Funding; *Genentech:* Research Funding; *Cephalon:* Research Funding; *Promedior:* Research Funding; *Constellation:* Consultancy, Research Funding; *Sierra Oncology:* Consultancy, Research Funding; *Incyte Corporation:* Consultancy, Research Funding; *CTI Biopharma Corp:* Research Funding; *Protagonist Therapeutics:* Research Funding; *ItalPharma:* Research Funding.

Kuykendall: *Incyte:* Consultancy; *Abbvie*: Honoraria; *Blueprint Medicines:* Honoraria; *Pharmaessentia*: Honoraria; *Novartis:* Honoraria and Speakers Bureau; *Protagonist Therapeutics*: Consultancy and Research Funding; *Celgene/BMS:* Honoraria.

Hoffman: *Forbius:* Consultancy; *Dompe:* Research Funding; *Protagonist:* Consultancy; *Abbvie:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an entity's Board of Directors or advisory committees

Ginzburg: *Protagonist Therapeutics:* Consultancy, Research Funding.

Gupta: *Protagonist:* Current Employment. Current equity holder in publicly-traded company

Valone: *Protagonist:* Consultancy and Current equity holder in publicly-traded company.

Khanna: *Protagonist:* Current Employment, Current equity holder in publicly-traded company.

Modi: *Protagonist:* Current Employment, Current equity holder in publicly-traded company.

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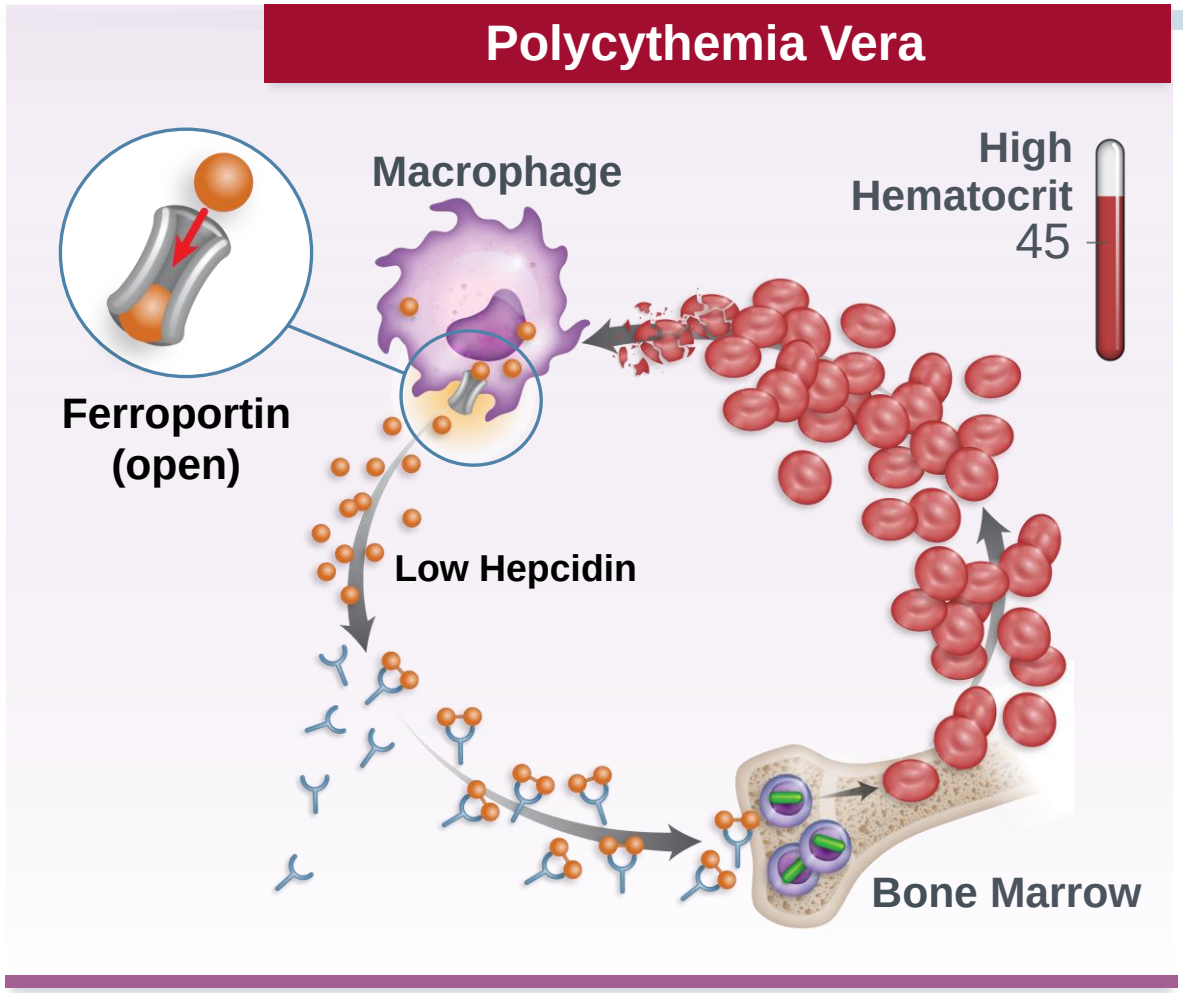
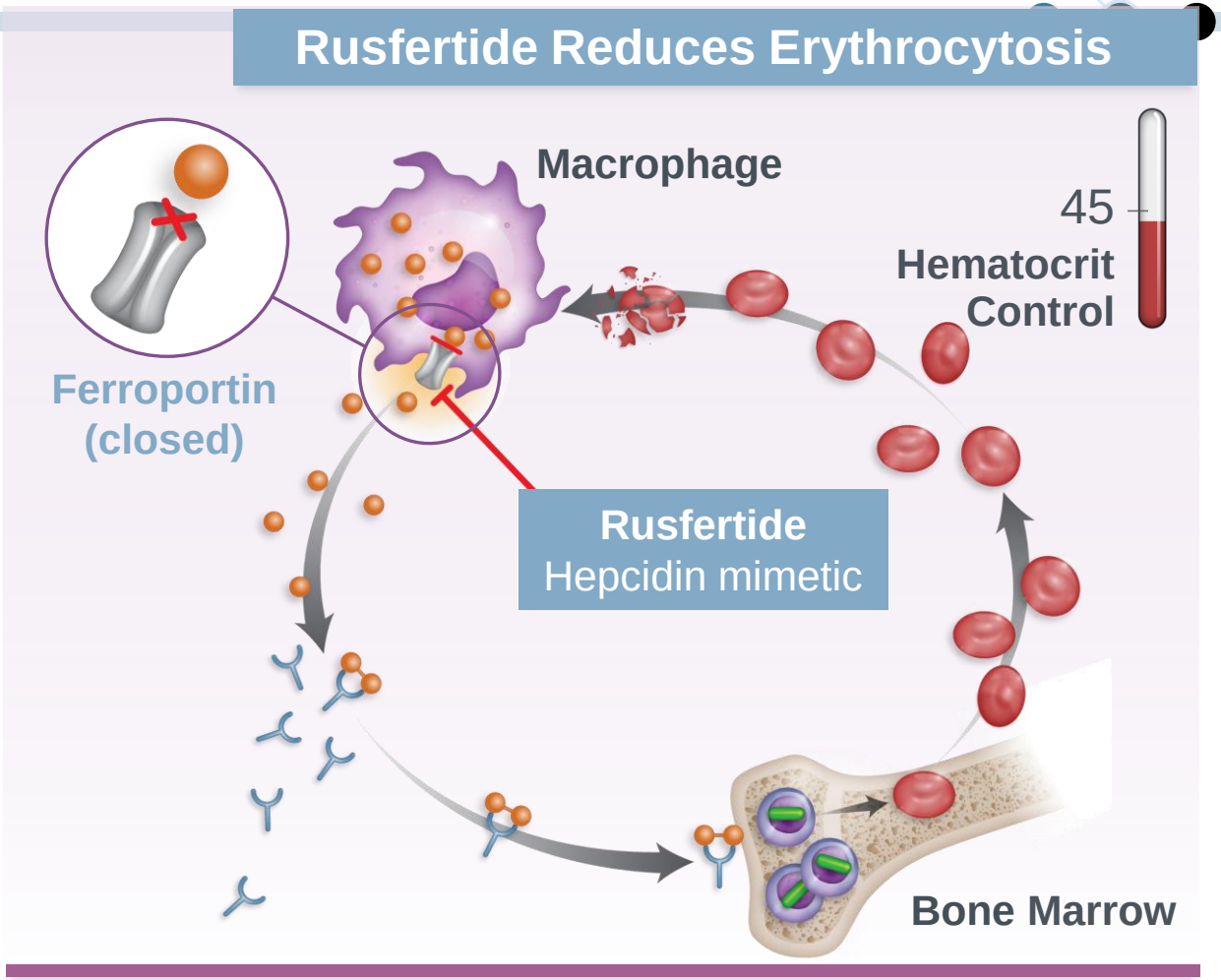
Introduction

- Polycythemia Vera (PV) is characterized by increased red blood cell production.
- PV patients likely spend significant time with hematocrit (HCT) >45% thereby increasing their risk of thrombosis.
- PV patients are treated with periodic therapeutic phlebotomy (TP) to maintain hematocrit levels <45% to reduce the incidence of thrombotic events.
- Symptomatic iron deficiency represents a challenge in PV as it is commonly present at diagnosis and worsens after repeated and/or frequent TP.
- Rusfertide, a hepcidin mimetic, presents an alternate mechanism of action to limit erythrocytosis, maintaining HCT <45%, essentially eliminating phlebotomies and reducing PV-related symptom burden.

Rusfertide Mechanism of Action





Transferrin (TF) Iron (Fe) TF-FE

Erythroblast JAK2 Red Blood Cell

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Phase 2 Data

- Two ongoing Phase 2 studies in PV subjects presented at ASH 2021* suggest that rusfertide could be an effective agent for treatment of PV, reversing iron deficiency and eliminating the need for TP in PV patients.
- Elimination of TP requirements for 18 months in TP-dependent PV subjects is significant. The effect of rusfertide on PV-related symptoms is also being evaluated.
- Rusfertide maintains HCT <45% and essentially eliminates TP in both low and high-risk PV patients.
- Rusfertide induction therapy with twice weekly dosing was also effective in rapidly achieving target hematocrit below 45% in PV subjects with elevated hematocrit.

* ***634. Myeloproliferative Syndromes: Dec 12, 2021***.

1. ***#388:*** *Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients*
2. ***#390:*** *Rusfertide (PTG-300) Induction Therapy Rapidly Achieves Hematocrit Control in Polycythemia Vera Patients without the Need for Therapeutic Phlebotomy*

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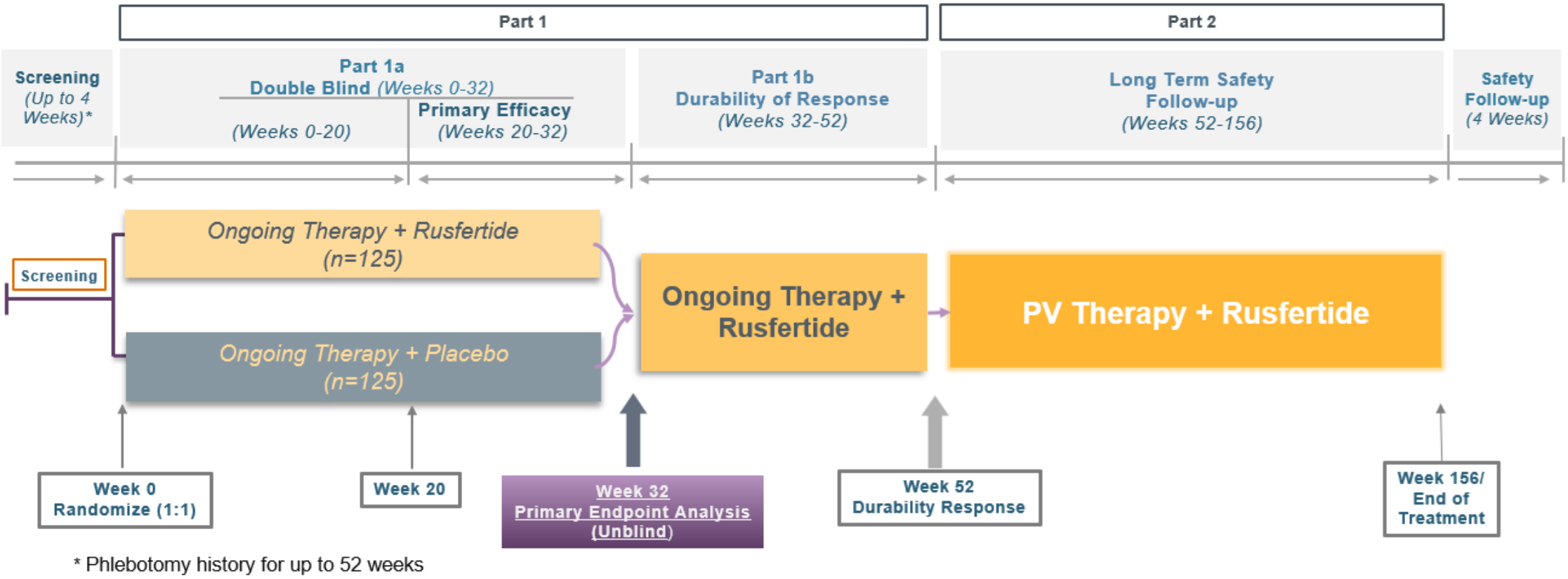
Double Blind Placebo-Controlled Phase 3 Study



250 PV Patients to be randomized across 100 Global sites- Dosing Starts in Q1, 2021

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Main Inclusion Criteria

Meet revised 2016 World Health Organization (WHO) criteria for the diagnosis of polycythemia vera.

Phlebotomy requiring defined as: (a) ≥3 phlebotomies due to inadequate hematocrit control in 6 months before randomization or at least 5 phlebotomies due to inadequate hematocrit control in 1 year before randomization, **and** (b) last phlebotomy due to inadequate hematocrit control within 3 months before randomization, **and** (c) no phlebotomy within 6 days prior to randomization.

Subjects may on stable regimen with Phlebotomy alone or in combination with cytoreductive agents (Hydroxyurea, Interferon and Ruxolitinib).

* *Other inclusion and exclusion criteria may apply*

Clinical Endpoints

Primary:

- Proportion of subjects achieving a response starting at Week 20 through Week 32 (inclusive) who receive rusfertide compared to placebo. Response is defined as absence of phlebotomy eligibility.

  Phlebotomy eligibility is defined as **either** a confirmed hematocrit ≥45% and that is at least 3% higher than the baseline hematocrit (value immediately prior to randomization at Week 0); confirmation required within 1 to 7 days, **or** a hematocrit ≥48%.

Key Secondary: Comparison of rusfertide to placebo

- Mean number of phlebotomies between Weeks 0 through 32 (inclusive).
- Proportion of subjects with all hematocrit values <45% between Week 0 through Week 32 (inclusive). A single transient hematocrit value ≥45% is allowed.
- Mean change from baseline in total fatigue score based on PROMIS Short Form 8a at Week 32.
- Mean change from baseline in total score based on Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) at Week 32.

Enrollment

- Total number of subjects to be randomized ~ 250
- Approximately 100 sites globally
- Study is expected to initiate enrollment in early 2022

A PHASE 3 STUDY OF HEPCIDIN MIMETIC RUSFERTIDE (PTG-300) IN PATIENTS WITH POLYCYTHEMIA VERA (PV)

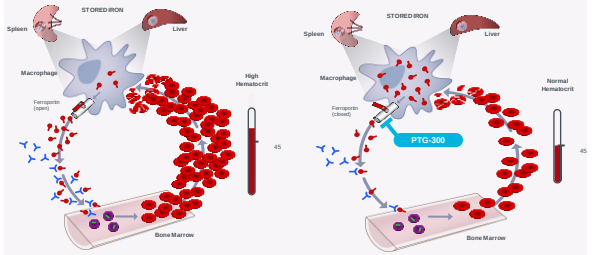
Authors: Srdan Verstovsek, MD PhD , Andrew Kuykendall, MD , Ronald Hoffman, MD , Yelena Ginzburg MD, Naveen Pemmaraju MD, Frank Valone MD, Nishit Modi PhD, Sarita Khanna PhD, Paula O'Connor MD, Suneel K Gupta PhD, Jean-Jacques Kiladjian MD, PhD

Background and Rationale

- Polycythemia Vera (PV) is characterized by increased red blood cell production
- PV patients likely spend significant time with hematocrit (HCT) > 45% thereby increasing their risk of thrombosis.
- PV patients are treated with periodic therapeutic phlebotomy (TP) to maintain hematocrit levels < 45% to reduce the incidence of thrombotic events.
- Symptomatic iron deficiency represents a challenge in PV as it is commonly present at diagnosis and worsens after repeated and/or frequent TP.
- Rusfertide, a hepcidin mimetic, presents an alternate mechanism of action to limit erythrocytosis, maintaining HCT <45%, essentially eliminating phlebotomies and reducing PV-related symptom burden.

Rusfertide Mechanism of Action

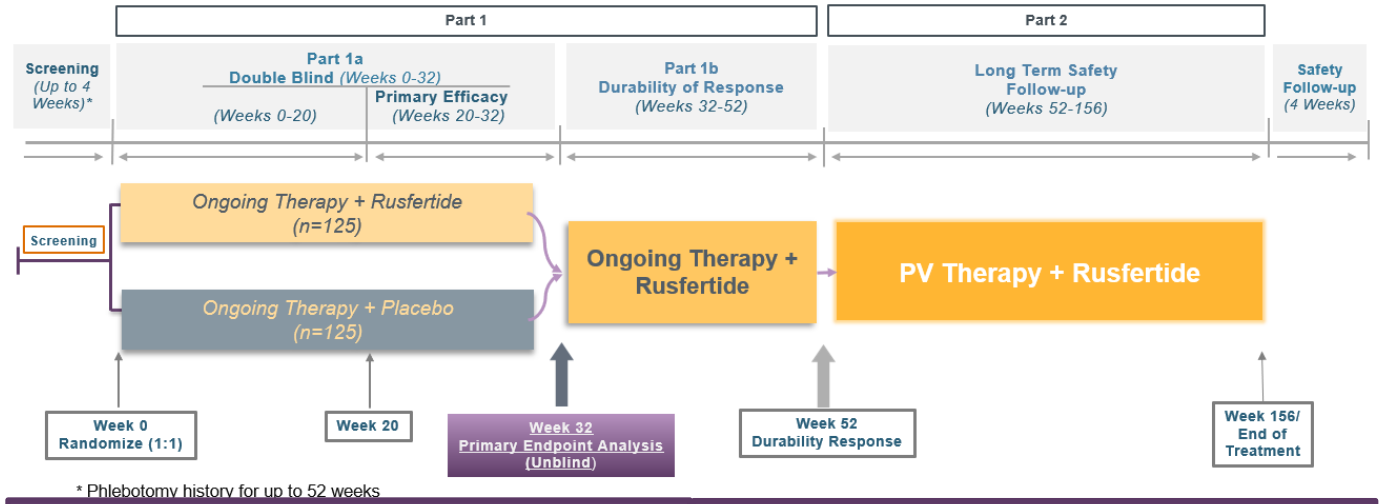
Polycythemia Vera: Rusfertide Reduces Erythrocytosis:



Rusfertide Data in Phase 2 PV Studies

- Two ongoing Phase 2 studies in PV subjects suggest that rusfertide could be an effective agent for treatment of PV, reversing iron deficiency and eliminating the need for TP in PV patients.
- Elimination of TP requirements for 6-8 months in TP-dependent PV subjects is significant. The effect of PTG-300 on PV-related symptoms is also being evaluated.
- Rusfertide maintains HCT < 45% and essentially eliminates TP in both low and high-risk PV patients.
- Rusfertide induction therapy with twice weekly dosing was also effective in rapidly achieving target hematocrit below 45% in PV patients with elevated hematocrit.

TRIAL DESIGN



* Phlebotomy history for up to 52 weeks

Objectives

Primary Objective:

To evaluate the safety and efficacy of rusfertide in subjects with polycythemia vera in maintaining hematocrit control.

Primary and Key Secondary Endpoints

Primary Efficacy Endpoint:

Proportion of subjects achieving a response starting at Week 20 through Week 32 (inclusive) who receive rusfertide compared to placebo.

Response is defined as absence of phlebotomy eligibility.

Phlebotomy eligibility is defined as **either** a confirmed hematocrit ≥45% and that is at least 3% higher than the baseline hematocrit (value immediately prior to randomization at Week 0); confirmation required within 1 to 7 days, **or** a hematocrit ≥48%.

Key Secondary Efficacy Endpoints: Rusfertide vs Placebo

1. Mean number of phlebotomies between Weeks 0 to 32 (inclusive)
2. Proportion of subjects with at least two hematocrit values ≥45% between Weeks 0 and 32 (inclusive)
3. Mean change from baseline in total fatigue score based on PROMIS Short Form 8a at Week 32
4. Mean change from baseline in total score based on MFSAF v4.0 at Week 32

Key Eligibility Criteria

Inclusion Criteria:

1. Meet revised 2016 World Health Organization (WHO) criteria for the diagnosis of polycythemia vera.
2. Phlebotomy requiring defined as: (a) ≥3 phlebotomies due to inadequate hematocrit control in 6 months before randomization or at least 5 phlebotomies due to inadequate hematocrit control in 1 year before randomization, **and** (b) last phlebotomy due to inadequate hematocrit control within 3 months before randomization, **and** (c) no phlebotomy within 6 days prior to randomization
3. Subjects may on stable regimen with Phlebotomy alone or in combination with cytoreductive agents (Hydroxyurea, Interferon and Ruxolitinib).

Exclusion Criteria:

1. Subjects who require phlebotomy at hematocrit levels lower than 45%
2. History of invasive malignancies within the last 5 years, except localized cured prostate cancer and cervical cancer
3. Subjects with non-invasive non-melanomatous skin cancer during screening unless adequately treated before randomization

- Total number of patients to be randomized approximately 250
- Approximately 100 sites Globally
- Study is expected to initiate enrollment in early 2022.

Protagonist Therapeutics

Protagonist Therapeutics

Poster Presentation 2

Rusfertide (PTG-300), a hepcidin memetic, maintains liver iron concentration in the absence of phlebotomies in patients with hereditary hemochromatosis

Poster Presentation:

Rusfertide (PTG-300), a Hepcidin Mimetic, Maintains Liver Iron Concentration in the Absence of Phlebotomies in Patients with Hereditary Hemachromatosis

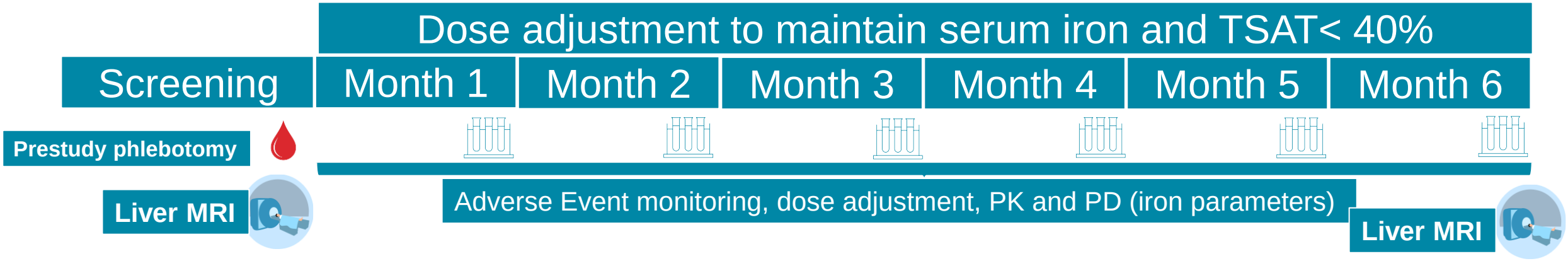
Kris Kowdley, MD, FAASLD
Director, Liver Institute Northwest, Seattle, WA
Clinical Professor
Elson S. Floyd College of Medicine
Washington State University

Protagonist Therapeutics

Introduction

- Hereditary hemochromatosis (HH) is an inherited iron overload disorder characterized by excessive absorption of iron, due to deficiency of hepcidin
- Patients with hereditary hemochromatosis (HH) require continued therapeutic phlebotomies to limit end-organ damage.
- Therapeutic phlebotomy is standard treatment for HH. While phlebotomy is effective, it does not target the biological mechanism, and may not be suitable for some patients.
- Rusfertide is a peptidic agent, structurally related to hepcidin, that mimics its inhibitory activity on ferroportin
- We conducted a Proof-of-Concept study to investigate the effect of rusfertide in patients with HH

Proof of Concept Study Design in Patients with Hereditary Hemochromatosis



Dosing	-	Subcutaneous, self-administered once or twice weekly. Dose adjusted based on TSAT and serum iron
Assessments	-	Adverse Events, PK, PD (iron parameters – TSAT, serum iron, ferritin, transferrin)
Phlebotomy	Within 7 days prior to dosing	As required on study. Criteria were serum ferritin levels and TSAT values higher than the pre-phlebotomy values at Screening or if Investigator deemed necessary for subject care
Liver MRI	Within 7 days prior to dosing	At end of 6-month study treatment
Endpoints		Safety, Reduction in phlebotomies, Serum iron, TSAT, transferrin, ferritin, Liver Iron Content by MRI

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Key Study Design Attributes

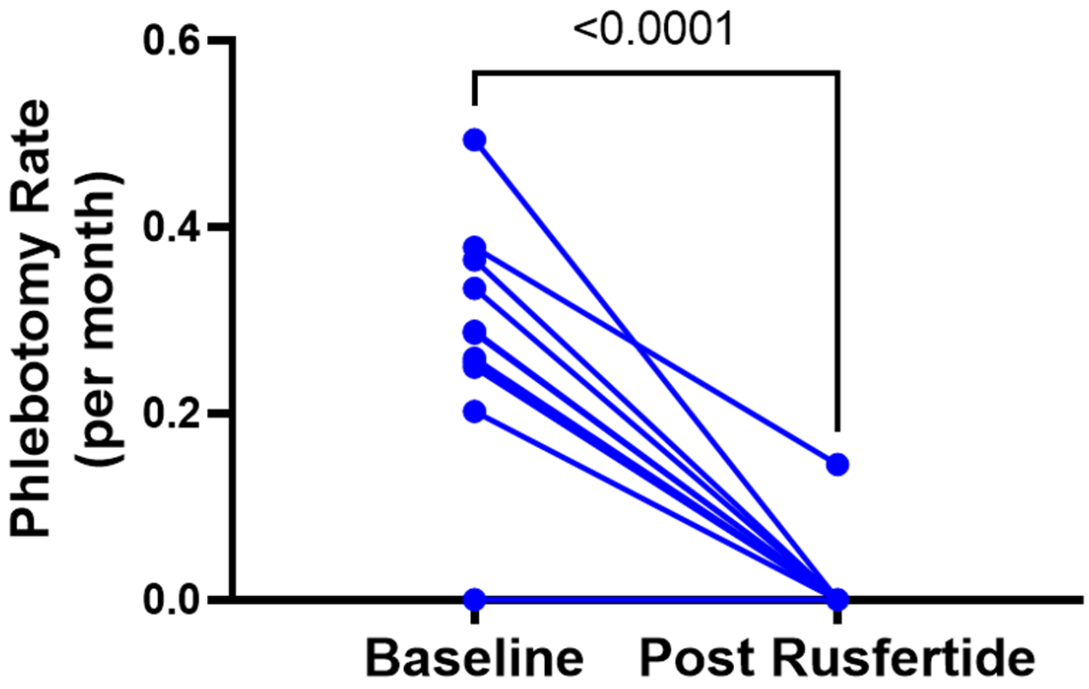
- Multicenter open-label study to investigate safety, tolerability pharmacokinetics and pharmacodynamics of subcutaneous Rusfertide
- Adult subjects with HFE-related hemochromatosis with prior genotype testing.
- Stable phlebotomy regimen for ≥6 months; receiving at least 3 phlebotomies over previous 12 months or at least 4 phlebotomies in previous 15 months and not more than 1 per month
- Serum ferritin <300 ng/mL
- Subjects with abnormal laboratory values, those receiving iron chelation therapy or erythrocytapheresis or with evidence of end-organ damage excluded

Baseline Characteristics

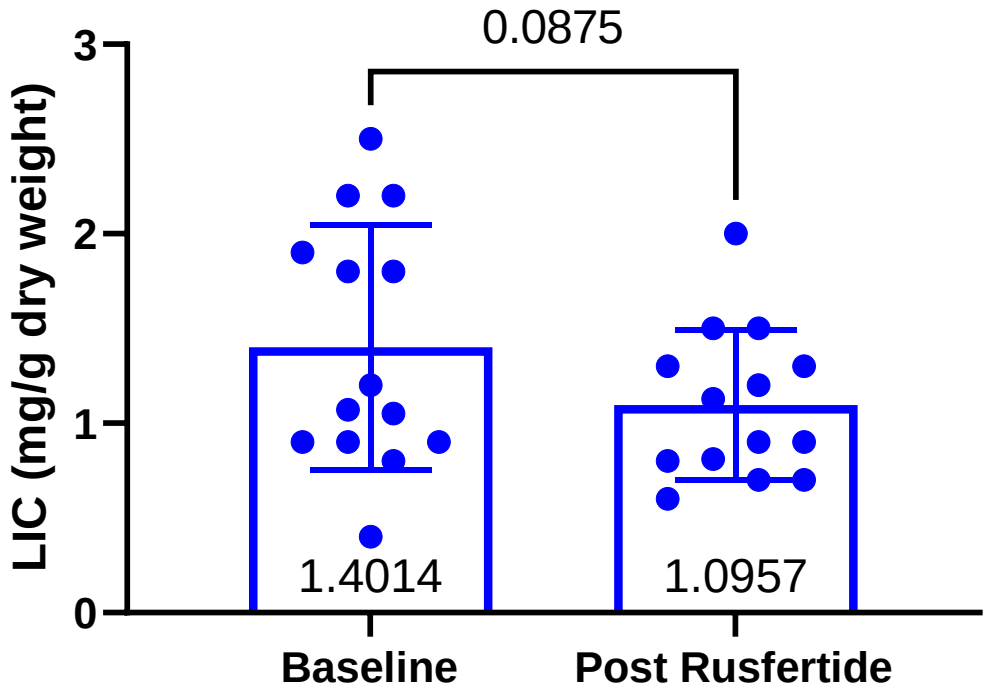
	Characteristic	Result (N=16)
Age, y (range)		62.5±12.3 (31-77)
	Age ≥ 65 y (%)	6 (37.5%)
Male, n (%)		10 (62.5%)
Years Since Diagnosis (range)		14.8±11.7 (2-43)
No of Phlebotomies in 24 weeks (range)		2.3±1.0 (1-4)
	3-4	7 (43.8%)
	1-2	9 (56.3%)
Serum Iron, mcg/dL (range)		137±60 (39-241)
TSAT, % (range)		43.1±23.7 (10-80)
Serum Ferritin, mcg/L (range)		82.3±57.6 (11.2-190.4)
Serum Transferrin, g/L (range)		2.3±0.4 (1.8, 3.1)

Rusfertide Reduces the Need for Phlebotomy and Controls Liver Iron Content (LIC) Measured by MRI

N=16



N=14



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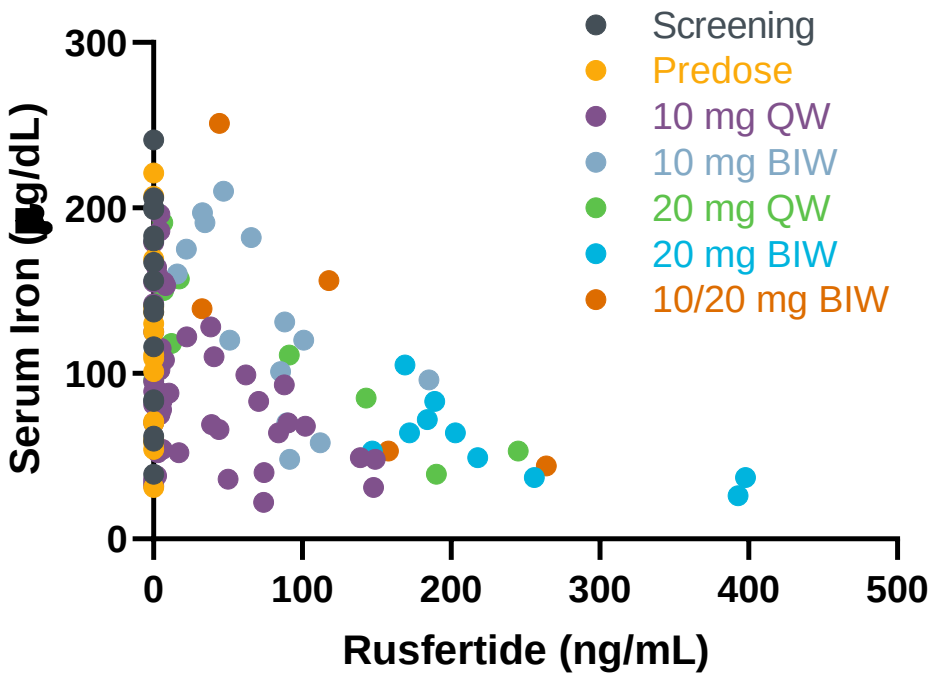
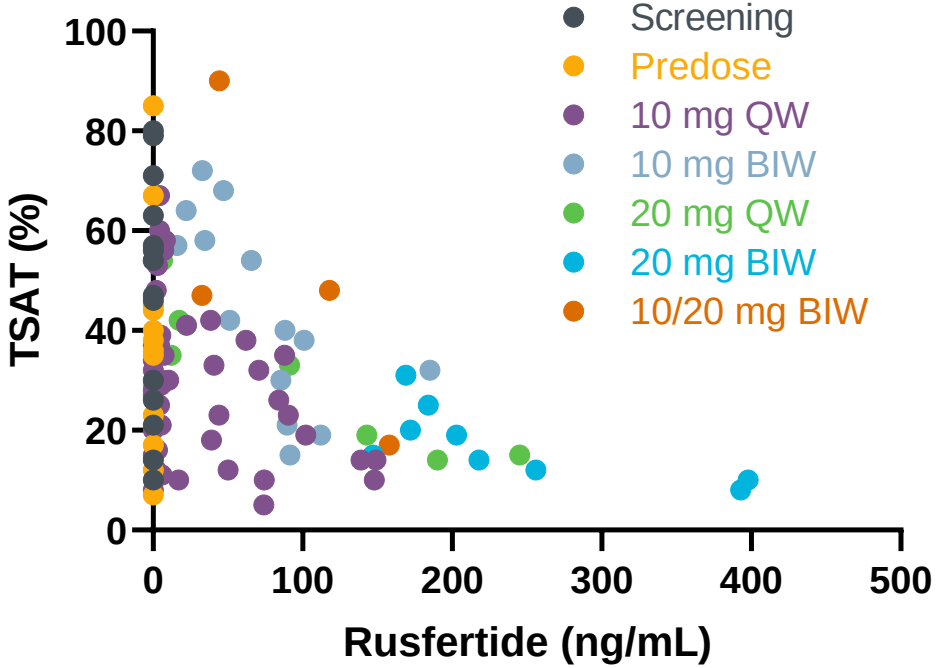
Exposure-Response Relationship for Rusfertide





- Rusfertide exhibits a dose regimen and concentration-dependent effect on serum iron and TSAT

Summary

- Consistent with the mechanism of action, rusfertide showed a dose- and concentration-dependent reduction in serum iron and transferrin saturation (TSAT)
- There was a significantly reduction in the number of phlebotomies
- Rusfertide controlled Liver Iron Content as determined by MRI
- Subcutaneous rusfertide was generally well-tolerated in patients with HH
  - Adverse events were commonly injection site reactions.
  - Adverse events were CTCAE Grade 1 or 2 except for one SAE of pancreatic adenocarcinoma that was considered pre-existing and not related to study drug
- The positive findings from this open-label proof of concept study in hereditary hemochromatosis patients merit further investigation in a controlled study

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Poster Presentation 3

Regulation of Iron Homeostasis and Efficacy of Rusfertide Analog Peptide in a Mouse Model for Polycythemia Vera

Regulation of Iron Homeostasis and Efficacy of Rusfertide Analog Peptide in a Mouse Model for Polycythemia Vera

Roopa Taranath, Li Zhao, Jayanthi Vengalam, Lawrence Lee, Tenny Tang, Celino Dion, Ahu Su, James Tovera, Ashok Bhandari, Xiaoli Cheng, Larry Mattheakis, David Liu

*All authors are employees and shareholders of Protagonist Therapeutics, Newark, Californ**ia***

Systemic Iron Modulation has Potential Disease Modifying Effects in Polycythemia Vera

- In polycythemia vera (PV), point mutation in JAK2 kinase (V617F) confers constitutive activity to JAK2 leading to excessive erythropoiesis that is independent of erythropoietin.
- PV patients present with elevated hematocrit, bone marrow erythroid hyperplasia, consequent dysregulated iron homeostasis, and iron deficiency due to chronic phlebotomy.
- Elevated hematocrit (HCT) and hyper-viscosity in the blood are risk factors for thrombosis and other symptoms. (Ref: Stein BL, J Clin Oncol, 2015)
- Iron restriction from erythropoiesis provides a mechanism for hematocrit control in PV, along with potential improvement in iron deficiency related to phlebotomy (Ref: Ginzburg YZ, Leukemia 2018).

Rusfertide is a subcutaneous injectable hepcidin mimetic, currently in clinical Phase2 studies in polycythemia vera and hereditary hemochromatosis

Rusfertide presentations at ASH2021:

Abstract #388: Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients. Presenting Author: Dr. Ronald Hoffman, MD

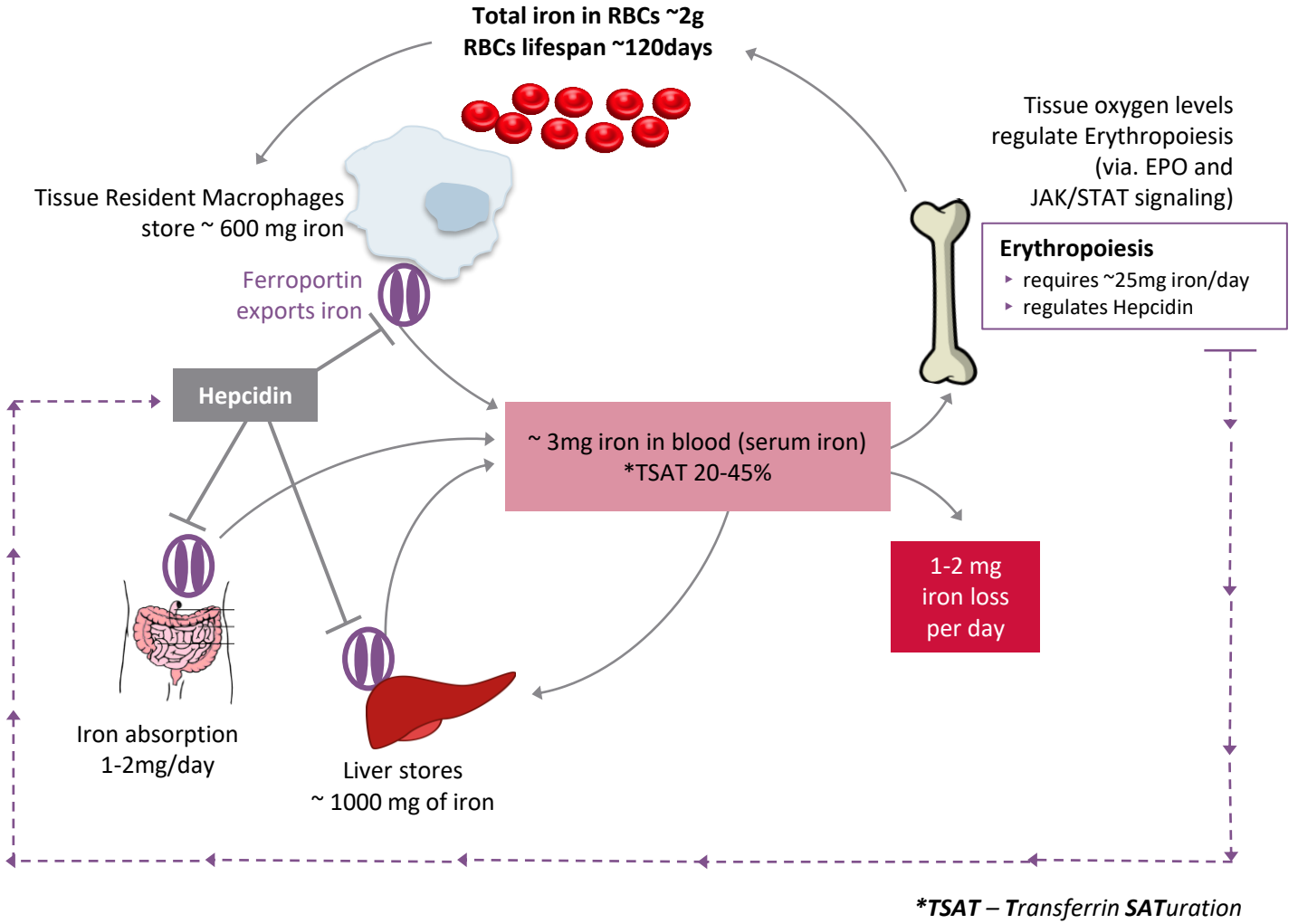
Abstract #390: Rusfertide (PTG-300) Induction Therapy Rapidly Achieves Hematocrit Control in Polycythemia Vera Patients without the Need for Therapeutic Phlebotomy. Presenting Author: Dr. Yelena Ginzburg, MD

Abstract #1504: A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera. Presenting Author: Dr. Srdan Verstovsek, MD, PhD

Abstract #943: Rusfertide (PTG-300), a Hepcidin Mimetic, Maintains Liver Iron Concentration in the Absence of Phlebotomies in Patients with Hereditary Hemochromatosis. Presenting Author: Dr. Kris V. Kowdley, MD

Systemic Iron Regulates Erythropoiesis

- Hepcidin targets iron exporter ferroportin, causing its internalization and subsequent degradation
  - Macrophages which recycle iron from senescent RBCs are the primary source of iron for erythropoiesis
- Rusfertide, a hepcidin mimetic, targets ferroportin.
  - thereby, restricting iron availability for erythropoiesis
- Pharmacodynamic effect of lowered serum iron can achieve hematocrit reduction in pre-clinical models. *(Taranath 2020; ASH meeting)*
- In this presentation, we show that a rusfertide analog Peptide A is effective in controlling hematocrit in mouse model for polycythemia vera.



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Polycythemia Vera Mouse Model and Study Design

Mouse model for polycythemia vera (PV) *(Ref: Mullaly A. et. al. Cancer Cell 2010)*

- Used $Jak2^{+/VF}$ heterozygous mice *(JAX stock #031658)*
  - carry an inverted Jak2 exon14 harboring a V to F mutation (V617F), in addition to its endogenous exon 14 of Jak2, flanked by loxP and loxP511 sites
- $Jak2^{+/VF}$ mice were cross-bred with Vav-iCre hemizygous mice *(JAX stock #008610)*
  - Cre mediated inversion and expression of the Jak2V617F mutant form, specifically in the hematopoietic compartment
- Wild Type (WT) C57BL/6 mice were non-lethally irradiated and transplanted with bone marrow from Jak2V617F mice (age and sex-matched)

Bone Marrow Transplantation
- **4 weeks for PV disease development**

PV mice treated for 6 weeks with 2.5 or 7.5 mg/kg *Peptide A (SQ injection; thrice a week)
- Controls: Vehicle treated PV and WT mice

**Peptide A: Rusfertide analog peptide with similar pharmacodynamic effects.*

Analysis:
- **Hematology for all Red Blood Cell parameters**
- **Serum and tissue iron concentrations.**
- **Flow cytometry analysis of bone marrow and spleen cells**

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Red Blood Cell Parameters were Normalized with Peptide A Treatment at the Minimum Efficacious Dose of 2.5 mg/kg

- Red Blood Cell (RBC)-counts, hemoglobin and hematocrit were significantly reduced in the 2.5 mg/kg Peptide A treated PV group as compared to PV-Vehicle.
- Treatment with higher dose of Peptide A at 7.5 mg/kg, resulted in lower-than-normal values for all the RBC parameters, indicating exaggerated pharmacology at this higher dose.
  - This group also showed lower-than-normal MCH and MCHC, indicating iron-deficient erythropoiesis

Improvement in hematology parameters in PV mouse model with Peptide A treatment for 6-weeks (thrice per week; TIW)

Groups	RBC† (10^6/µL)			HGB† (g/dL)			HCT† (%)			MCH† (pg)			MCHC† (g/dL)			MCV† (fL)		
	Mean	SD	p‡	Mean	SD	p‡	Mean	SD	p‡	Mean	SD	p‡	Mean	SD	p‡	Mean	SD	p‡
WT† Vehicle	10.3	± 0.3	****	14.3	± 0.5	****	50.4	± 0.9	****	13.9	± 0.1	ns	28.6	± 1.0	ns	49.2	± 1.1	ns
PV† Vehicle	15.2	± 1.7	-	20.2	± 0.7	-	77.6	± 3.6	-	13.4	± 1.5	-	26.1	± 1.1	-	51.6	± 6.2	-
PV† - Peptide A 2.5 mg/kg	11.1	± 1.4	****	16.1	± 0.9	****	52.8	± 9.1	****	14.6	± 1.5	ns	31.2	± 4.5	*	47.3	± 3.8	ns
PV† - Peptide A 7.5 mg/kg	7.3	± 1.4	****	8.3	± 2.1	****	42.7	± 4.9	****	11.2	± 1.1	**	19.3	± 3.1	***	59.1	± 5.6	*

† *WT- Wild Type Mice; PV- Polycythemia Vera Mice; RBC- Red Blood Cell counts; HGB- Hemoglobin; HCT- Hematocrit; MCH- Mean Corpuscular Hemoglobin; MCHC-Mean Corpuscular Hemoglobin Concentration; MCV- Mean Corpuscular Volume*

‡ Statistical analysis were performed using One-way ANOVA with post-hoc Dunnet's Multiple comparisons vs. PV-Vehicle group; ns- non-significant p>0.05; * p<0.05; ** p<0.01; *** p<0.001; ****p<0.0001

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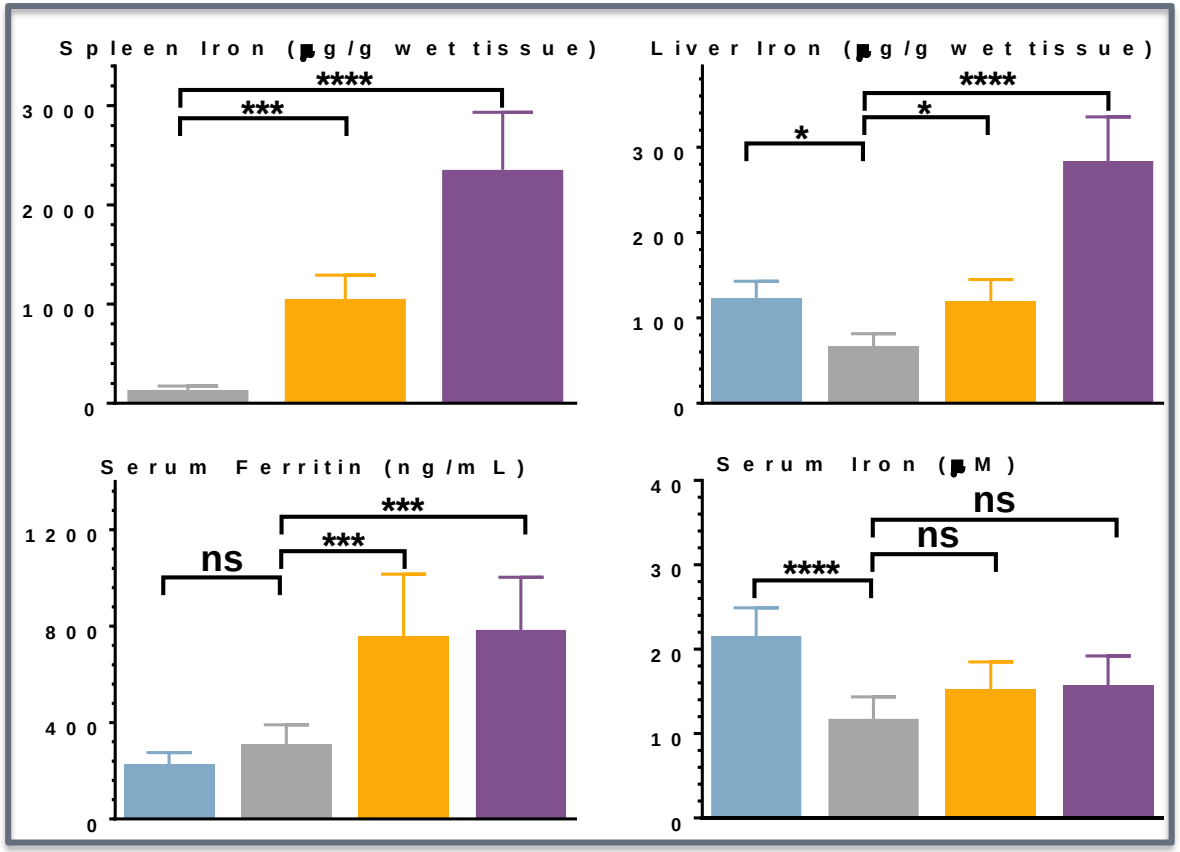
Iron Sequestration in the Spleen and Liver with Peptide A Treatment

- Significant increases in spleen iron concentration with Peptide A treatment
- Significant increase in liver iron in 7.5 mg/kg high dose group.
- Elevated serum ferritin, without any increase in serum iron (measurements after drug washout).



Statistical analysis:
One-way ANOVA w/Dunnett's Multiple Comparisons;
*ns p>0.5, * p<0.5, ** p<0.01, *** p<0.001, **** p<0.0001*

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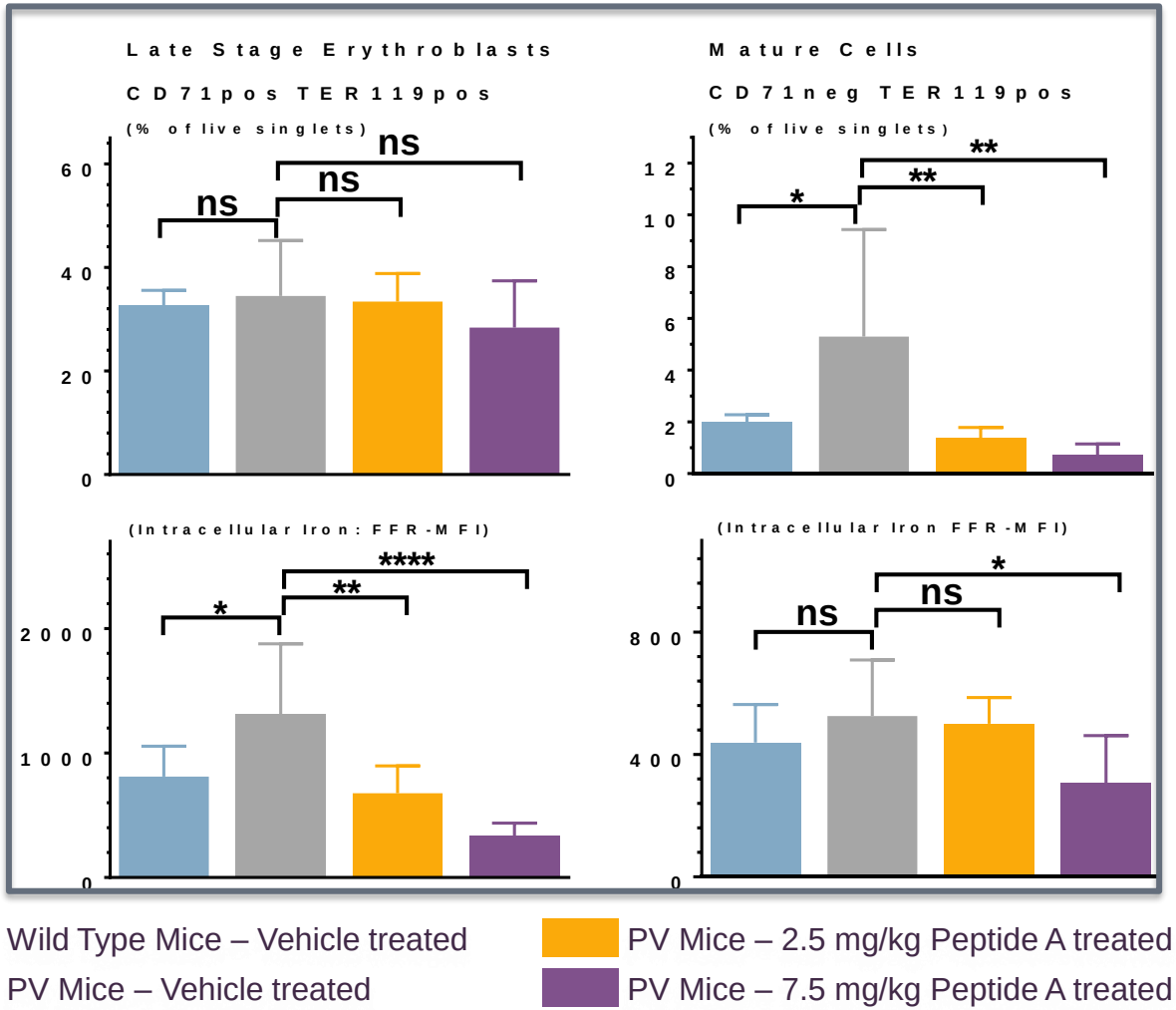
CD71neg TER119pos Mature Cells in Bone Marrow were Significantly Reduced With Peptide A Treatment

- Late-stage erythroblast (CD71pos TER119pos) were not increased significantly in PV mice.
- Reductions in the intracellular iron in both populations with Peptide A treatment.



CD71: *(Transferrin-Receptor) expressed on erythroblasts before maturation;* ***TER119****: expressed on late-stage erythroblasts and mature erythrocytes;* ***FFR:*** *FerroFarRed™ dye (cell permeable iron binder);* ***MFI****: Median Fluorescence Intensity;* ***F4/80 and CD11bInt****: Splenic Red Pulp Macrophage markers;* ***pos****: positive;* ***neg****: negative;* ***Int****: Intermediate*
Statistical analysis: *One-way ANOVA w/Dunnett's Multiple Comparisons; ns p>0.5, * p<0.5, ** p<0.01, *** p<0.001, **** p<0.0001*

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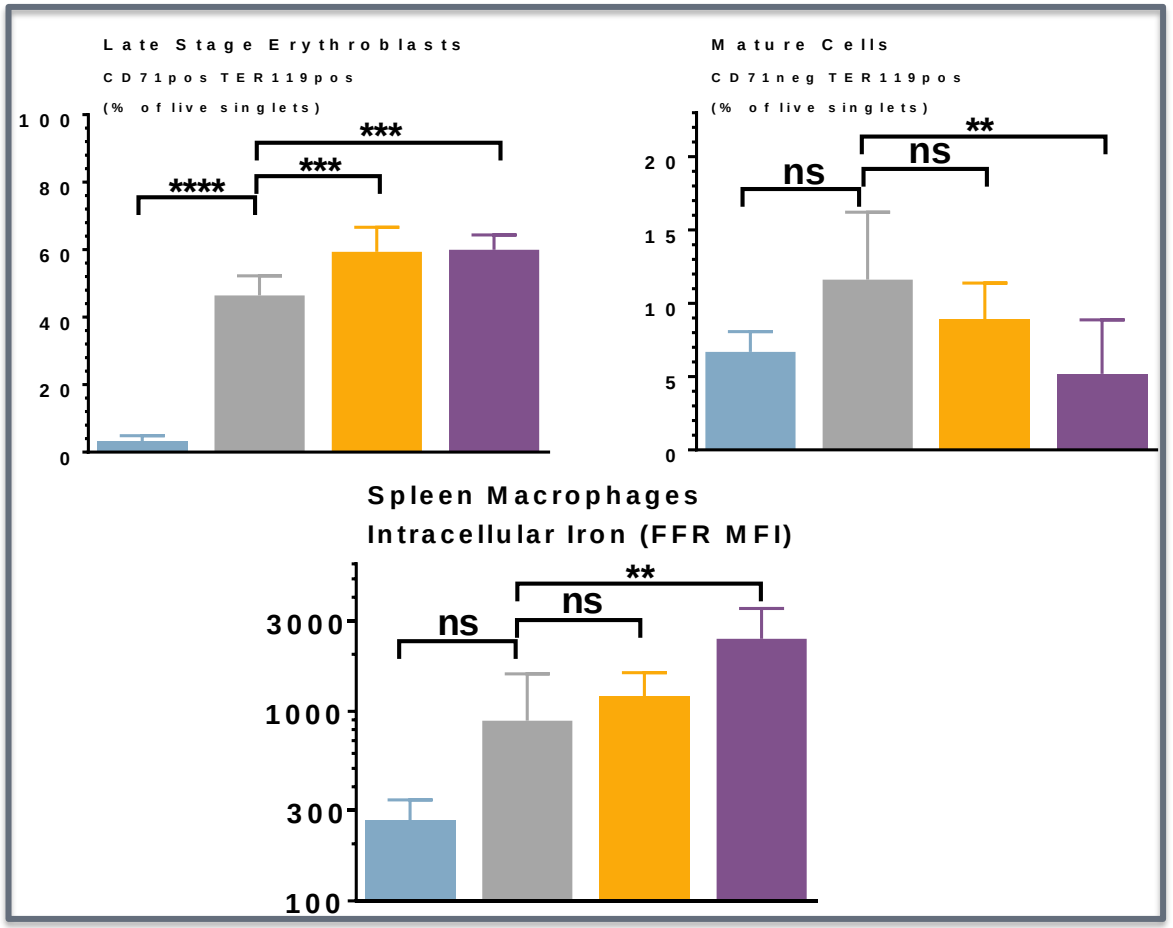
CD71neg TER119pos Mature Cells in Spleen were Significantly Reduced With 7.5 mg/kg Peptide A Treatment

- No reductions were observed in CD71pos TER119pos late-stage erythroblasts.
- Dose dependent reduction in mature erythrocytes correlates well with dose-dependent reduction of RBC-counts in circulation.
- Intracellular iron (measured using iron-sensitive FFR dye) in splenic macrophages (F4/80pos CD11bInt) is higher in PV mice
  - no changes with Peptide A treatment, except small increase in 7.5 mg/kg treated group.



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Statistical analysis: *One-way ANOVA w/Dunnett's Multiple Comparisons; ns p>0.5, * p<0.5, ** p<0.01, *** p<0.001, **** p<0.0001*

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Conclusions

- We present results from studies in a mouse PV model with JAK2-V617F mutation as in human PV.
- Rusfertide analog Peptide A is efficacious in lowering hematocrit (HCT) while modulating other hematological parameters.
- We show dose dependent increase in iron sequestration in spleen and liver.
- Further, we show redistribution of iron away from erythropoiesis as demonstrated by reduction in mature erythrocytes in bone marrow and spleen, in conjunction with reduced iron in bone marrow erythroblasts.

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THANK YOU