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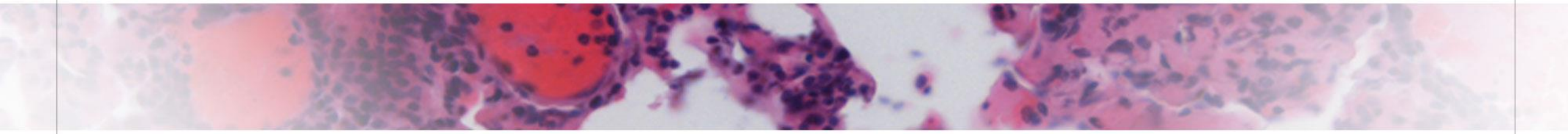


Durability of Hematocrit Control in Polycythemia Vera With the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results From the REVIVE Study

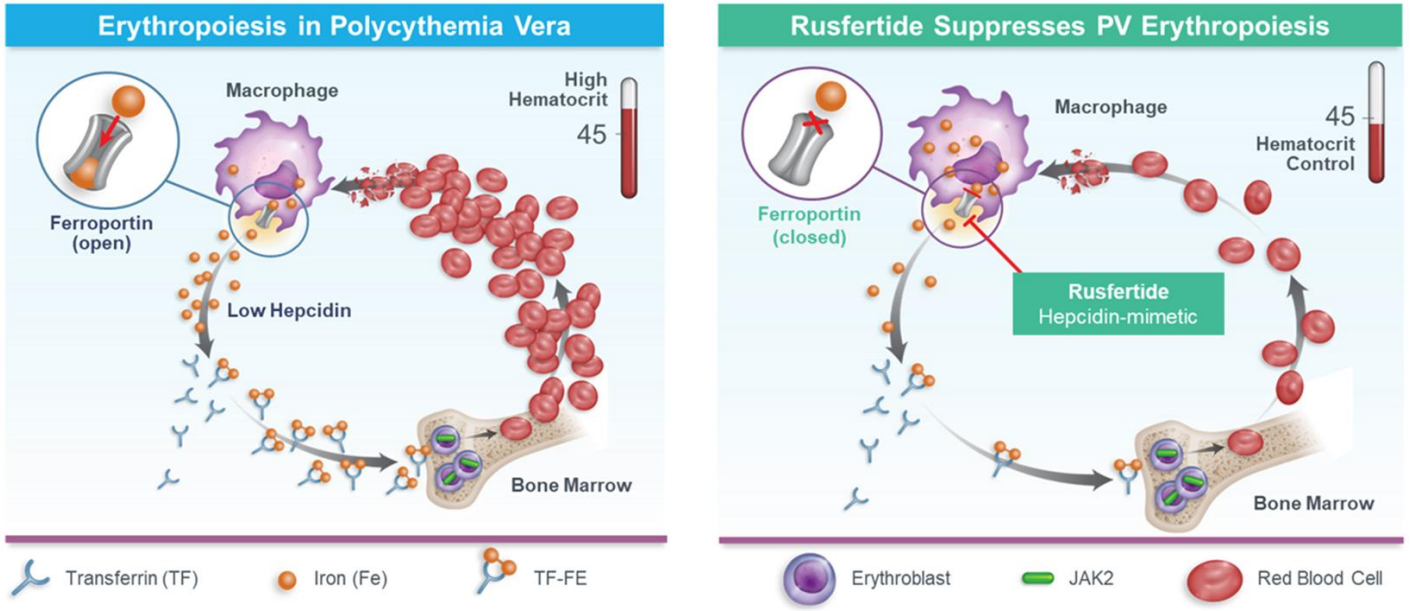
Presenter: Ellen K Ritchie, MD

Ellen K Ritchie, MD[1]; Kristin Marie Pettit, MD[2]; Andrew T. Kuykendall, MD[3]; Marina Kremyanskaya, MD, PhD[4]; Naveen Pemmaraju, MD[5]; Sarita Khanna, PhD[6] Arturo Molina, MD, MS, FACP[6]; and Suneel Gupta, PhD[6]

[1]Weill Cornell Medical College, Cornell University, New York, NY; [2]Department of Internal Medicine, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI; [3]Moffitt Cancer Center, Tampa, FL; [4]Division of Hematology & Medical Oncology, Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai, New York, NY; [5]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Protagonist Therapeutics, Inc., Newark, California

Background: Polycythemia Vera and Rusfertide

- PV is an MPN associated with uncontrolled erythrocytosis, systemic symptoms, and an increased risk of thromboembolic and cardiovascular complications[1,2]
  - These characteristics are largely driven by uncontrolled HCT levels
- Rusfertide is a hepcidin mimetic that controls red blood cell production in PV patients by limiting iron availability[3]



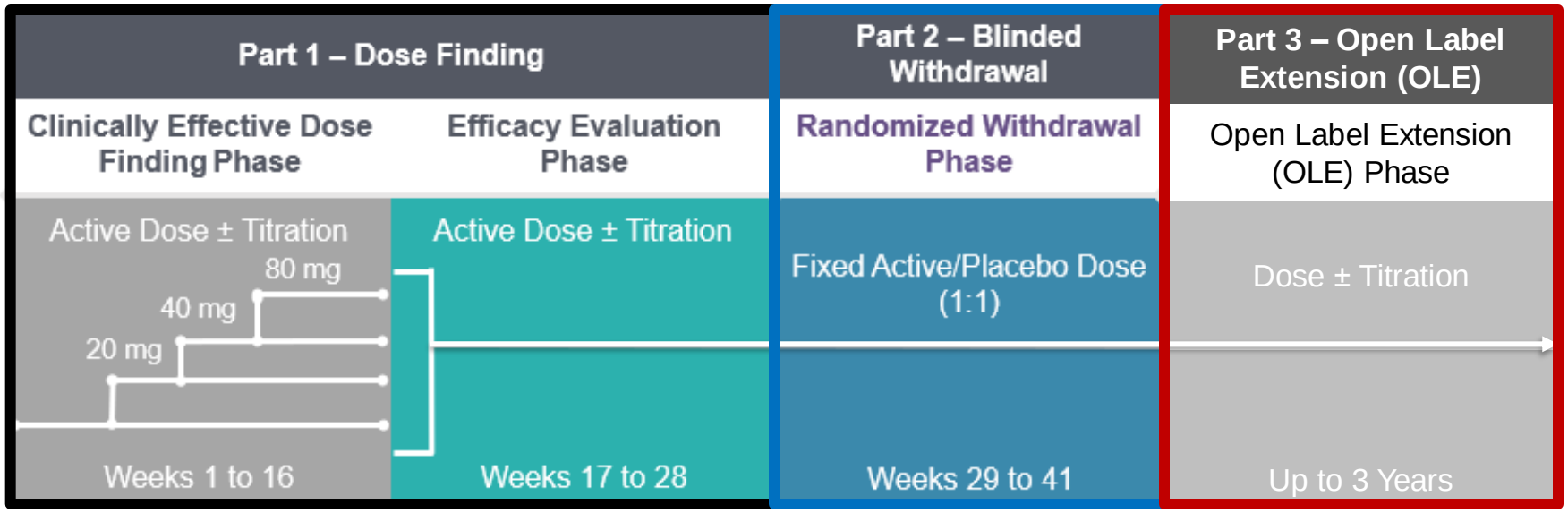
HCT, hematocrit; JAK2, Janus Kinase 2; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

1. Kuykendall AT. Ann Hematol. 2023. 2. Mora B, Passamonti F. Clin Lymphoma Myeloma Leuk. 2023;23(2):79-85. 3. Kremyanskaya M, et al. EHA2023. (Abstract LB2710).

Data cutoff: 17 October 2023

REVIVE: Background and Study Design

- The phase 2 REVIVE trial (PTG-300-04; NCT04057040) is investigating the safety and efficacy of rusfertide in phlebotomy-dependent patients with PV treated with or without concurrent cytoreductive therapy



- Eligibility: patients are required to have PV and ≥3 therapeutic phlebotomies in the 28-week period prior to enrollment with or without concurrent cytoreductive therapies
- Phlebotomy prior to study entry to achieve hematocrit <45%

- REVIVE was designed to evaluate the efficacy of rusfertide therapy
  - Part 2 (i.e., randomized withdrawal phase) was especially conducive to measuring efficacy

OLE, open-label extension; PV, polycythemia vera.
Adapted from Kremyanskaya M, et al. EHA2023. (Abstract LB2710).

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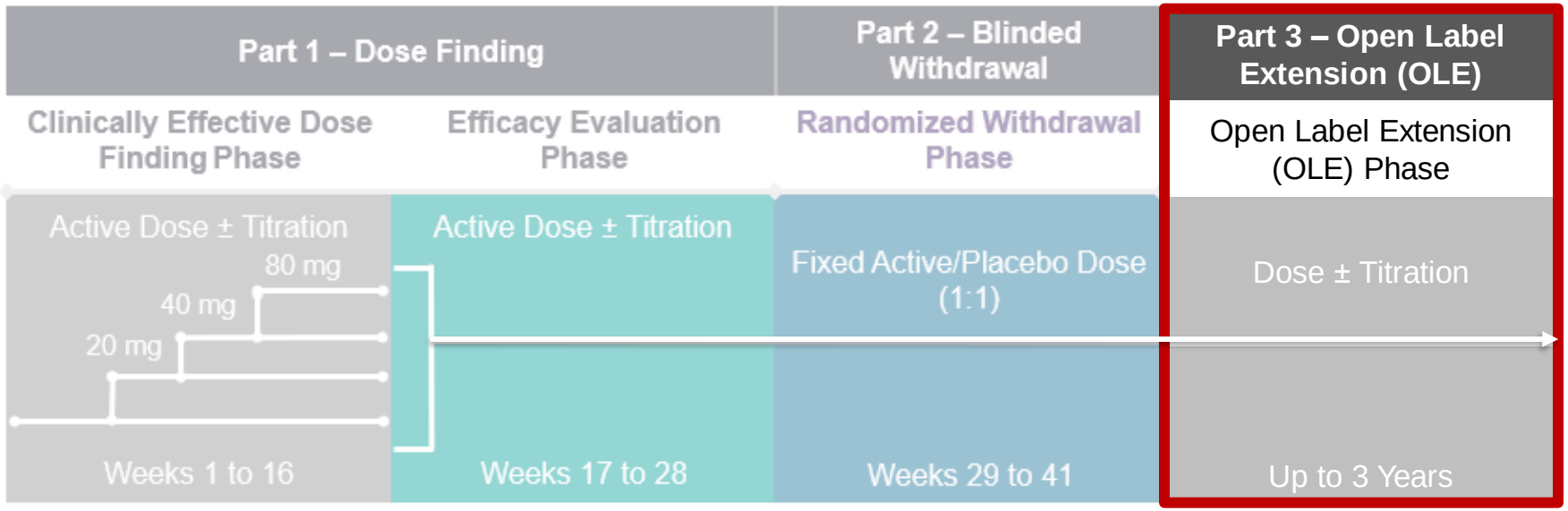

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- REVIVE was designed to evaluate the efficacy of rusfertide therapy
  - Part 2 (i.e., randomized withdrawal phase) was especially conducive to measuring efficacy
- **The primary objective of this presentation is to share long-term follow up results from patients who continued into the OLE phase (Part 3) of REVIVE**

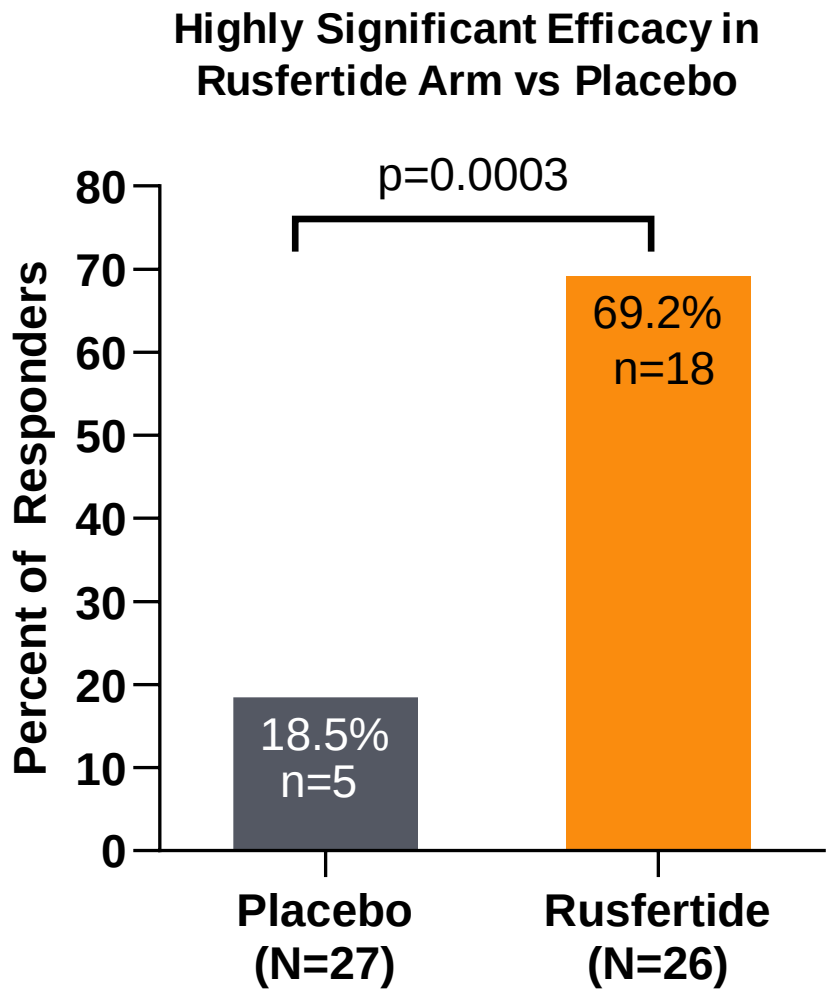
OLE, open-label extension; PV, polycythemia vera.
Adapted from Kremyanskaya M, et al. EHA2023. (Abstract LB2710).

Data cutoff: 17 October 2023

REVIVE Part 2: Blinded Randomized Withdrawal Phase (Weeks 29-41)

Primary Efficacy Endpoint Met[1]

- The response rate* was 69.2% (18 out of 26 patients) in rusfertide-treated patients
  - 8 patients were non-responders per protocol
    - All 8 non-responders continued in Part 3 (OLE) of REVIVE
- In the placebo arm, the response rate* was 18.5% (5 out of 27 patients)
- Response rates with rusfertide were superior to placebo irrespective of whether patients received cytoreductive therapy
- 92.3% of patients (24 out of 26) in the rusfertide arm did not receive phlebotomy compared with 44.4% (12 out of 27) in the placebo arm



OLE, open-label extension.

Adapted from Kremyanskaya M, et al. EHA2023. (Abstract LB2710).

Data cutoff: 17 October 2023

REVIVE Part 3: Demographics and Disease Characteristics

- In REVIVE, 58 of the 70 patients who enrolled onto Part 1 continued onto Part 3 (OLE)
  - As of 17 October 2023, 57 (81.4%) patients have been treated for ≥1 year, 51 (72.9%) for ≥1.5 years, and 37 (52.9%) for ≥2 years

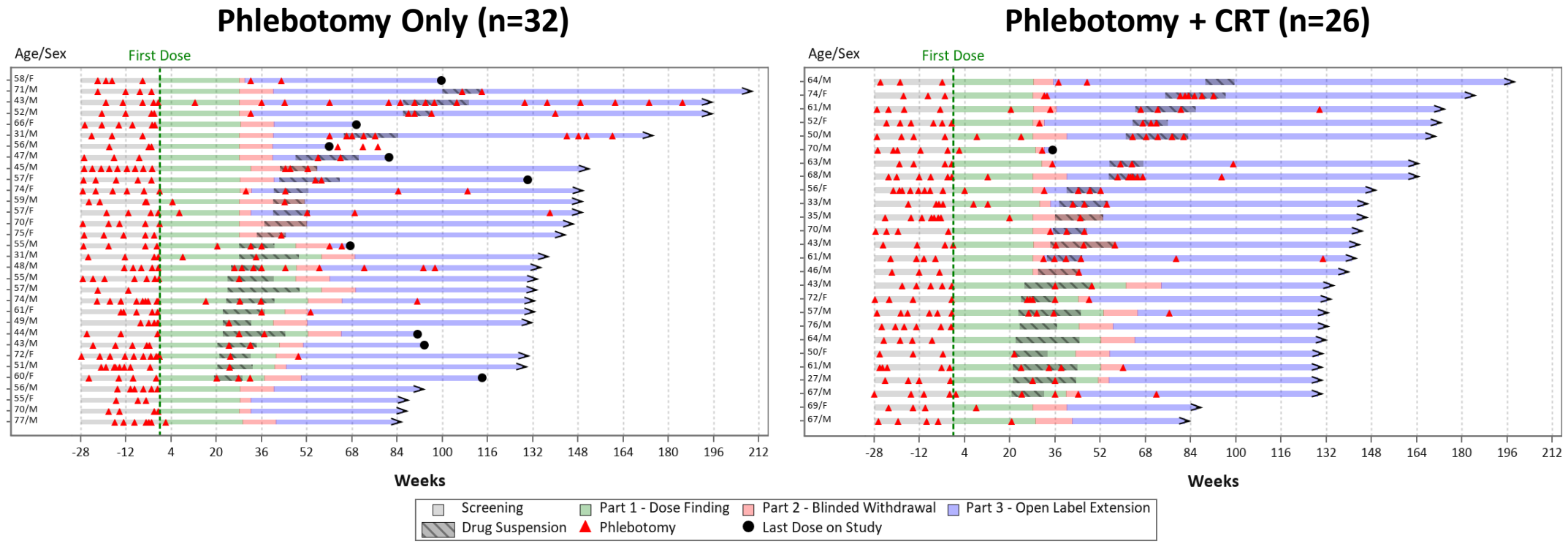
	Part 1	Part 2 (N=59)		Part 3
	Rusfertide	Placebo	Rusfertide	Rusfertide
	N=70	n=29	n=30	N=58
Age (years), median (range)	58 (27-77)	61 (33-77)	56 (27-76)	57 (27-77)
Gender, n (%)				
Male	49 (70.0)	18 (62.1)	24 (80.0)	41 (70.7)
Female	21 (30.0)	11 (37.9)	6 (20.0)	17 (29.3)
Risk, n (%)				
High Risk	40 (57.1)	18 (62.1)	13 (43.3)	30 (51.7)
Low Risk	30 (42.9)	11 (37.9)	17 (56.7)	28 (48.3)
Disease Characteristics				
Age at PV diagnosis (years), median (range)	55 (5-74)	58 (29-73)	54 (26-74)	55 (26-74)
PV duration (years), median (range)	2.5 (0-35)	3.4 (1-18)	2.1 (0-22)	2.3 (0-22)
Phlebotomy History – 28 weeks prior to rusfertide treatment				
Number of phlebotomies, mean ± SD	4.7 ± 1.6	4.8 ± 1.6	4.7 ± 1.6	4.7 ± 1.6
Requiring ≥5 phlebotomies, n (%)	30 (42.9)	14 (48.3)	13 (43.3)	26 (44.8)
Concurrent Therapy, n (%)				
Phlebotomy only	37 (52.9)	12 (41.4)	20 (66.7)	32 (55.2)
Phlebotomy + cytoreductive therapy	33 (47.1)	17 (58.6)	10 (33.3)	26 (44.8)

OLE, open-label extension; PV, polycythemia vera; SD, standard deviation.

Data cutoff: 17 October 2023

Rusfertide Decreased the Frequency of Therapeutic Phlebotomy With or Without Concurrent Cytoreductive Therapy

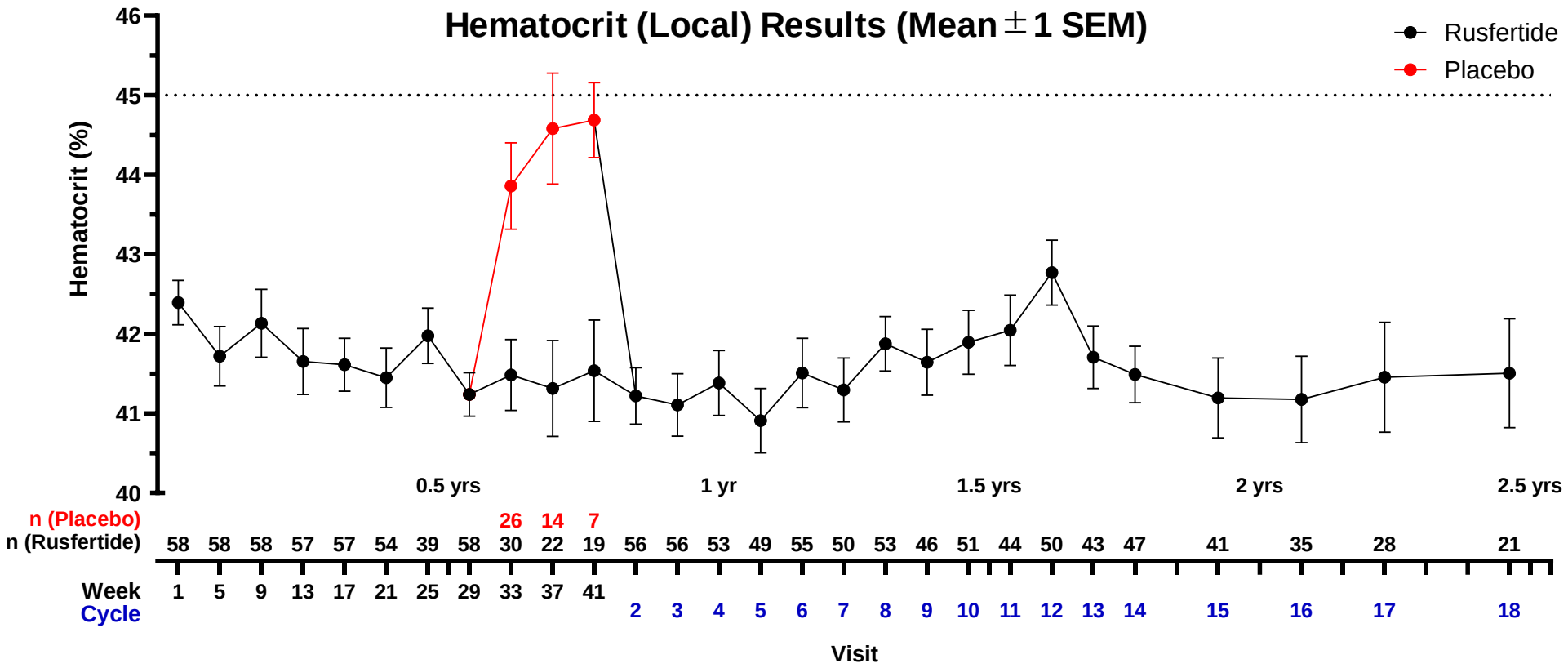
- In patients who continued onto Part 3, 32 (55.2%) and 26 (44.8%) patients were treated with phlebotomy alone or phlebotomy with CRT, respectively
  - Of those patients receiving phlebotomy with CRT, 13 (22.4%) received hydroxyurea, 7 (12.1%) received interferon, 5 (8.6%) received a JAK inhibitor, and 1 patient (1.7%) received hydroxyurea and interferon



CRT, cytoreductive therapy.

Data cutoff: 17 October 2023

Rusfertide Provided Durable Control of Hematocrit Through 2.5 Years

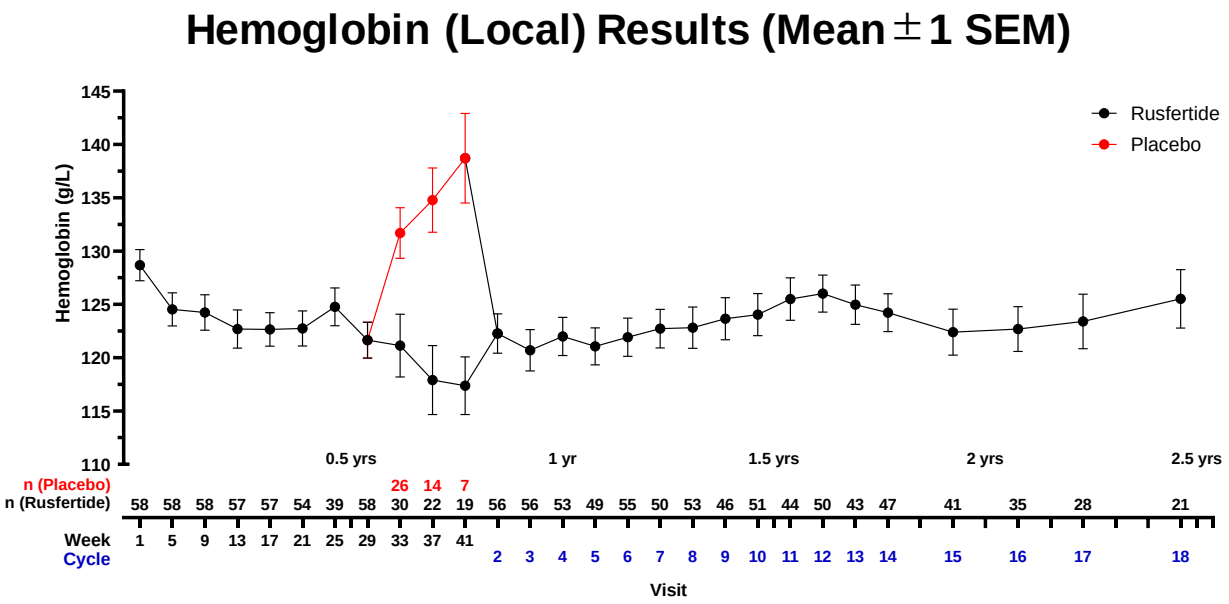


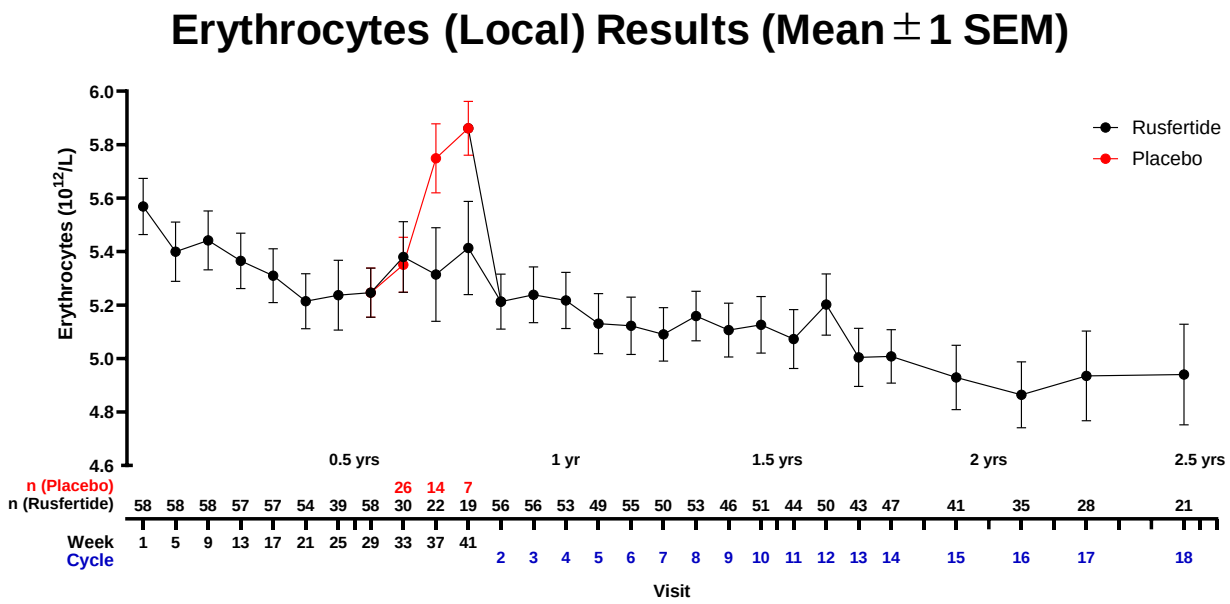
- Rusfertide treatment resulted in consistent maintenance of hematocrit <45%

Dotted horizontal line, hematocrit <45%.
SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

Mean Hemoglobin Levels Generally Remained Stable and Mean Erythrocyte Counts Decreased Through 2.5 years





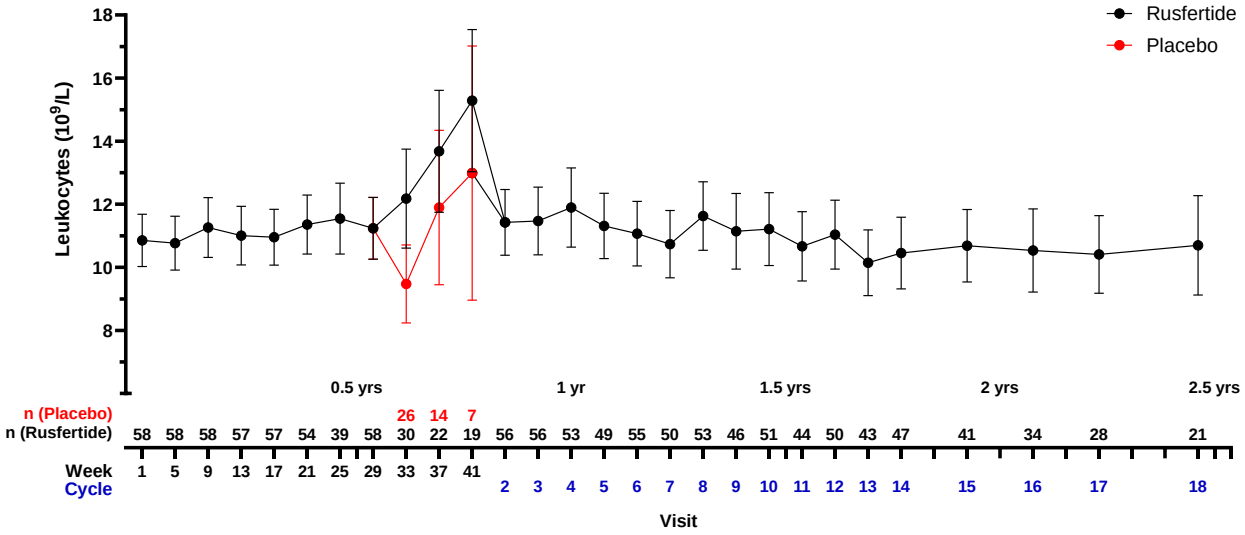
- Mean hemoglobin levels and mean erythrocyte counts increased when rusfertide treatment was held or discontinued during the blinded randomized withdrawal period (Part 2)

SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

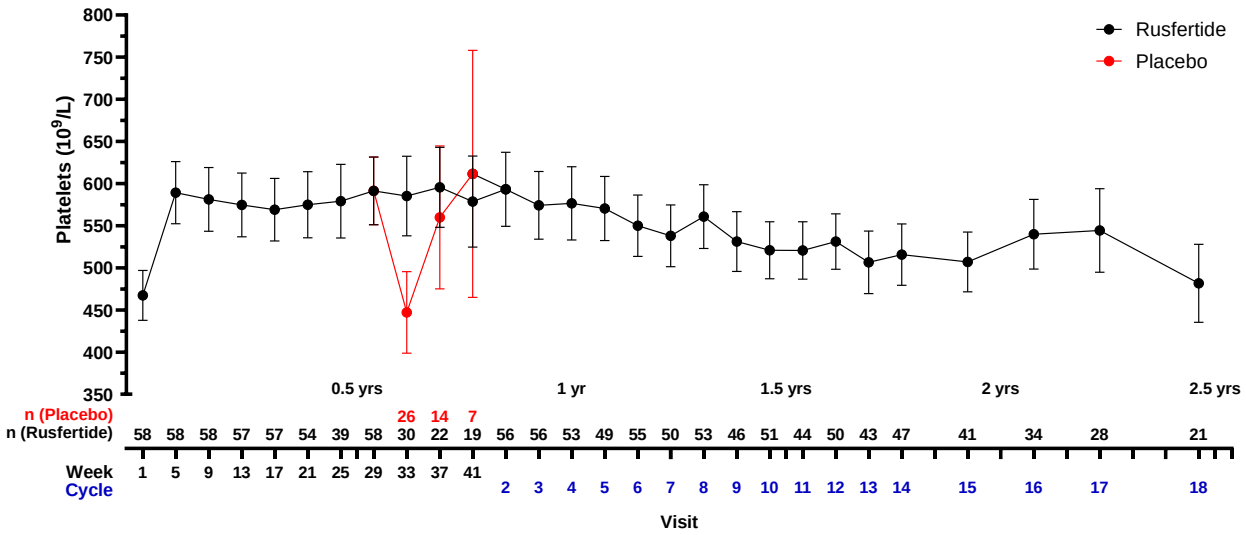
Leukocytes Were Stable; Platelet Counts Increased During Initial Treatment and Remain Stable Over Time

Leukocytes (Local) Results (Mean ± 1 SEM)



- Mean leukocyte counts remained stable and did not change meaningfully over the duration of the trial

Platelets (Local) Results (Mean ± 1 SEM)

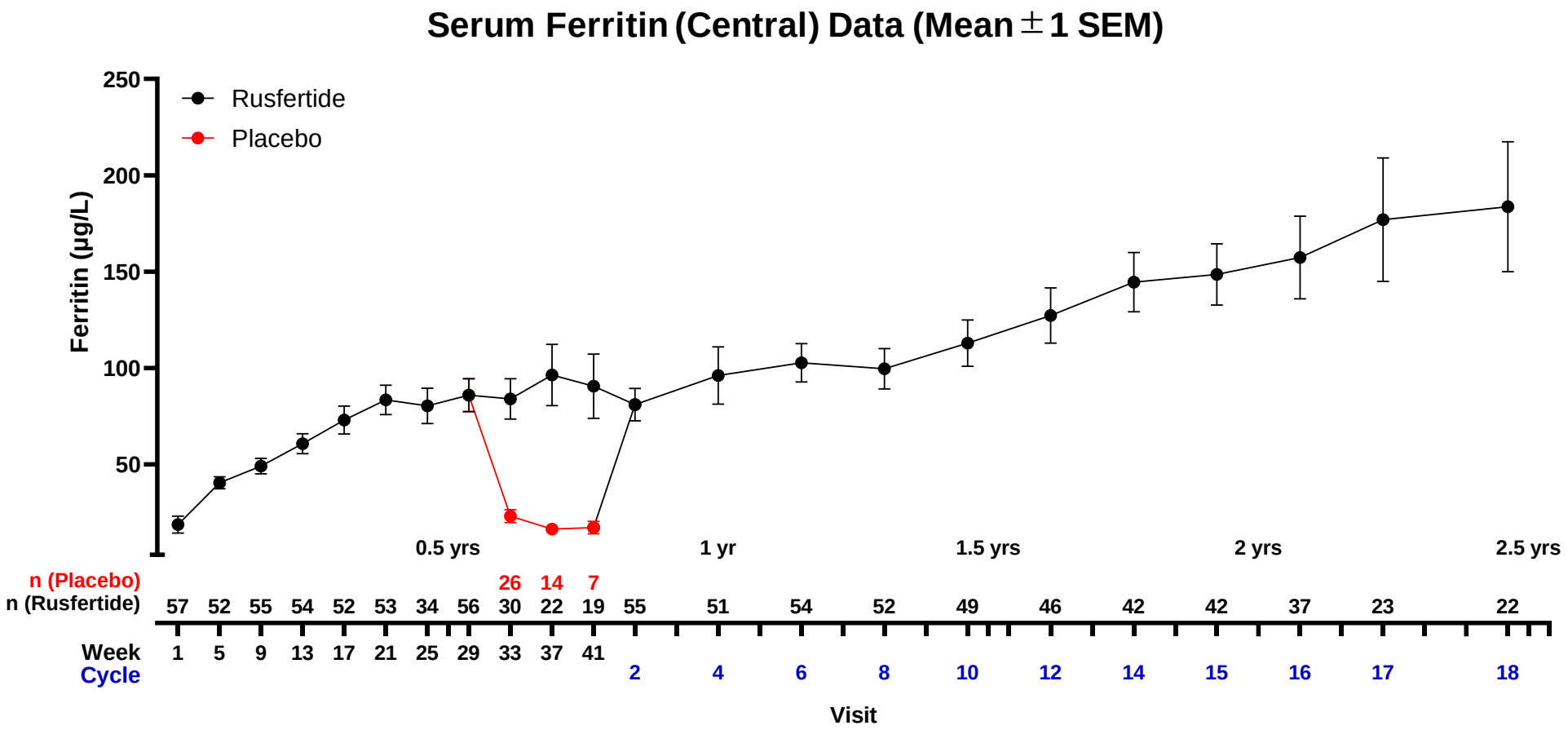


- After increasing by approximately 30% post-baseline, mean platelet counts stabilized over time

SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

Rusfertide Resulted in Normalization of Serum Ferritin Levels Over 2.5 Years



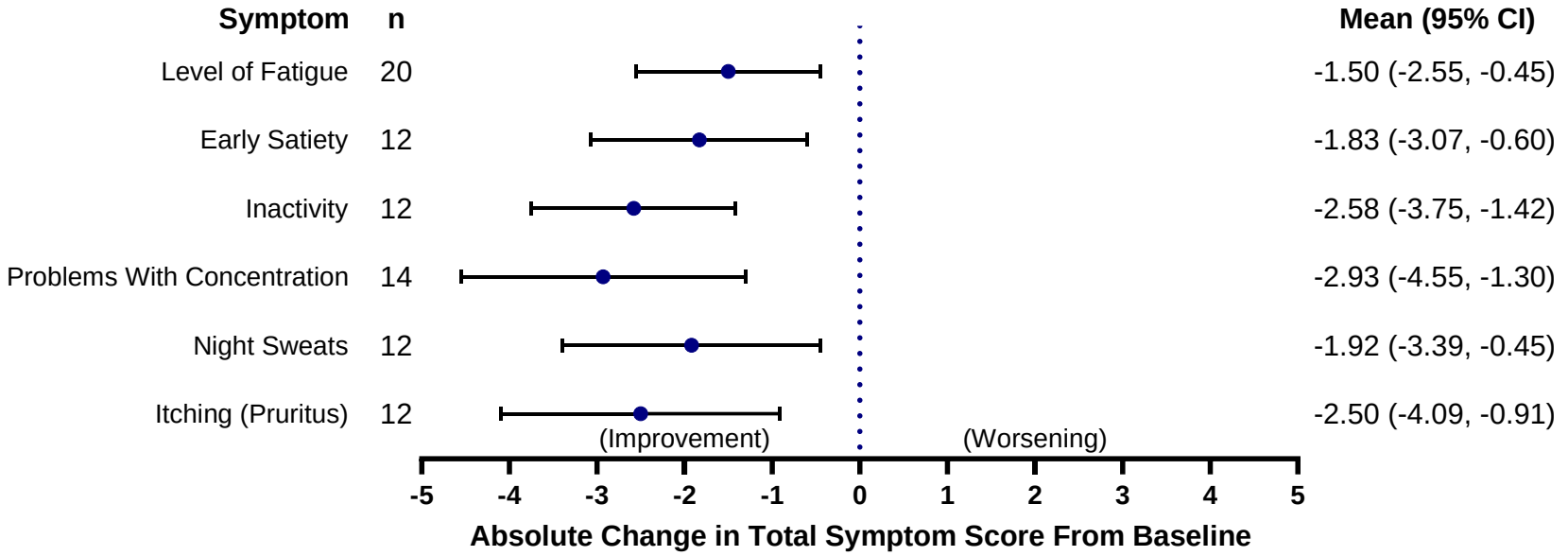
- Prior to enrollment, iron-related parameters were consistent with systemic iron deficiency

SEM, standard error of the mean; yr, year; yrs, years.

Data cutoff: 17 October 2023

REVIVE Part 1: Rusfertide Improved Patient-Reported Outcomes

- In Part 1, PROs were assessed using the MPN-SAF TSS
  - Mean change from Baseline (Week 1) to Week 29 of ISSs from the MPN-SAF for patients with moderate (score, 4-6 out of 10) to severe symptoms (score, 7-10 out of 10) at Baseline
  - In patients with moderate or severe ISSs at Baseline (≥4 out of 10), rusfertide significantly decreased symptoms in fatigue, early satiety, night sweats, problems with concentration, inactivity, and itching



Error bars represent 95% CIs around the mean change from baseline. No multiplicity adjustments were made for analyses for all the supportive efficacy endpoints. Symptoms presented are limited to those with at least 10 patients.

CI, confidence interval; ISS, individual symptom score; MPN-SAF, myeloproliferative neoplasm symptom assessment form; PROs, patient-reported outcomes.

Data cutoff: 17 October 2023

REVIVE: Long-Term Safety Profile of Rusfertide – No New Safety Signals

Summary of Reported TEAEs (Any Grade) in ≥10 Patients (Overall)

TEAEs (Any Grade) by Preferred Term, n (%)	Part 1 N=70	Part 2		Part 3 n=58	Overall (N=70)
		Placebo n=29	Rusfertide n=30		
Patients with at least 1 TEAE	69 (98.6)	16 (55.2)	24 (80.0)	51 (87.9)	70 (100.0)
Injection site erythema	46 (65.7)	2 (6.9)	7 (23.3)	23 (39.7)	**46 (65.7)**
Injection site pain	25 (35.7)	1 (3.4)	3 (10.0)	6 (10.3)	**28 (40.0)**
Injection site pruritus	26 (37.1)	0	4 (13.3)	11 (19.0)	**28 (40.0)**
Fatigue	16 (22.9)	1 (3.4)	1 (3.3)	8 (13.8)	23 (32.9)
Injection site mass	17 (24.3)	0	2 (6.7)	12 (20.7)	**21 (30.0)**
Arthralgia	13 (18.6)	0	0	7 (12.1)	19 (27.1)
Pruritus	14 (20.0)	3 (10.3)	2 (6.7)	7 (12.1)	19 (27.1)
Injection site swelling	15 (21.4)	0	4 (13.3)	8 (13.8)	**18 (25.7)**
COVID-19	5 (7.1)	1 (3.4)	0	13 (22.4)	17 (24.3)
Dizziness	10 (14.3)	0	0	8 (13.8)	17 (24.3)
Headache	11 (15.7)	2 (6.9)	0	7 (12.1)	16 (22.9)
Nausea	11 (15.7)	2 (6.9)	1 (3.3)	6 (10.3)	16 (22.9)
Anemia	12 (17.1)	0	0	6 (10.3)	15 (21.4)
Injection site irritation	11 (15.7)	0	4 (13.3)	9 (15.5)	**14 (20.0)**
Injection site bruising	9 (12.9)	1 (3.4)	2 (6.7)	6 (10.3)	**11 (15.7)**
Diarrhea	7 (10.0)	1 (3.4)	0	5 (8.6)	10 (14.3)
Dyspnea	6 (8.6)	2 (6.9)	1 (3.3)	5 (8.6)	10 (14.3)
Hyperhidrosis	5 (7.1)	0	0	6 (10.3)	10 (14.3)
Injection site warmth	9 (12.9)	0	0	3 (5.2)	**10 (14.3)**

- The most common TEAEs were injection site reactions, which were localized and grade 1-2 in severity and decreased in incidence
- Overall, 77.1% of TEAEs had a maximum grade of 2
- Overall, 21.4% of TEAEs were grade 3; there were no grade 4 or 5 TEAEs
- Overall, the median duration of exposure to rusfertide was 105.4 weeks (range, 3-182 weeks)

COVID-19, Coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Data cutoff: 17 October 2023

Serious Adverse Events – No New Safety Signals

- Overall, 14 patients (20.0%) experienced an SAE*
  - There were 3 cases of basal cell carcinoma
  - There was 1 case each of atrial fibrillation, myocardial infarction, anogenital dysplasia, constipation, non-cardiac chest pain, gastroenteritis, sepsis, lung adenocarcinoma, malignant melanoma, malignant melanoma (Stage I), acute myeloid leukemia (Part 2; placebo arm), squamous cell carcinoma (Part 2; placebo arm), ischemic stroke, syncope, transient ischemic attack, peripheral artery aneurysm, and peripheral vascular disorder
- The nature of the SAEs observed is consistent with comorbidities anticipated in the PV population, including vascular events and skin cancer

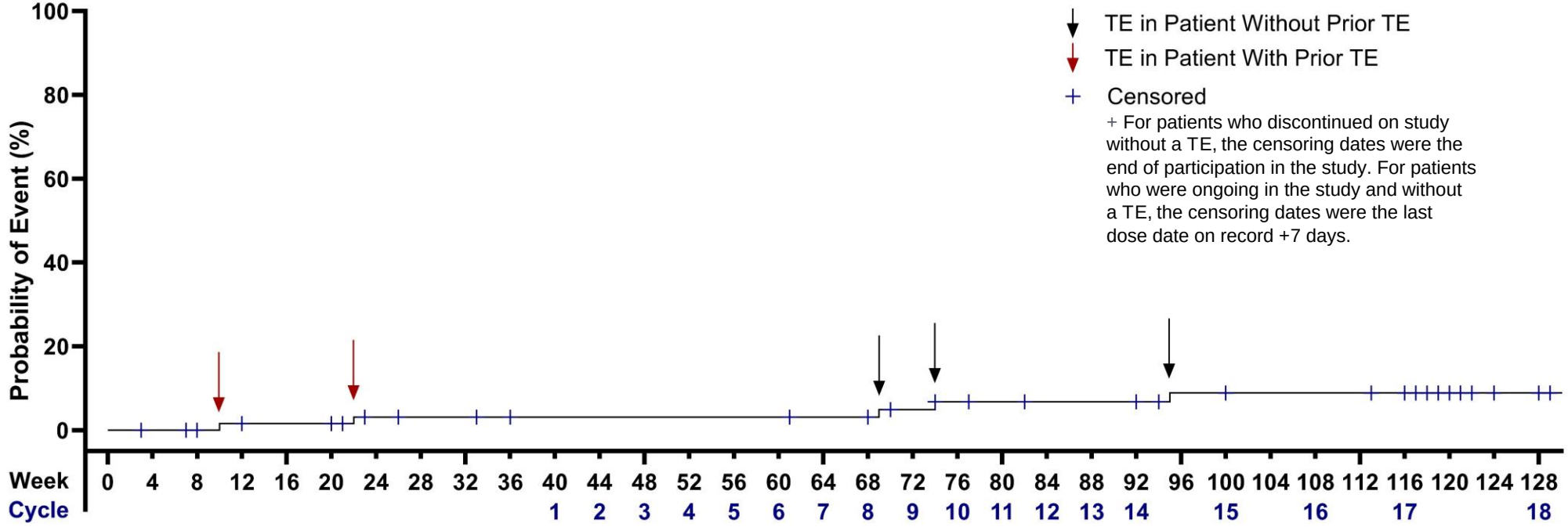
**Most SAEs were assessed as being unrelated to rusfertide by the investigators*

PV, polycythemia vera; SAE, serious adverse event.

Data cutoff: 17 October 2023

Time to Thrombotic Events (TEs): All TEs Occurred in High-Risk Patients

Five TEs Were Reported; All Occurred Before Week 100 (Cycle 15)



- Only 2 of 14 patients with a TE prior to study entry had a subsequent TE on study
  - These 2 TEs occurred relatively early in the study (Weeks 10 and 22)

TE, thrombotic event.

Data cutoff: 17 October 2023

Five Thrombotic Events (TEs) Were Reported on Study

All 5 TEs Occurred in High-Risk Patients; Most Had Additional Risk Factors

Age (Yrs)	Gender	PV Diagnosis	Risk Status	Prior History of TE	Diagnosis of Prior TE	Concurrent CRT at Study Entry	TE on Study	Additional Risk Factors	Onset of TE (Day)	Patient Status (Time Since First Rusfertide Dose, Days)
69	F	2005	High	Portal vein thrombosis	2021	HU	Acute myocardial infarction	Hypertension	70	Ongoing (Day 589)
68	F	2010	High	Myocardial Infarction	2020	HU	Superficial vein thrombosis	Hypertension, diabetes mellitus, high BMI	155	Discontinued (Day 190)
66	F	2012	High	None	NA	None	Pulmonary embolism	Dyslipidemia, smoking history	485	Discontinued (Day 487)
60	F	2017	High	None	NA	None	Transient ischemic attack	None	521	Discontinued (Day 799)
72	F	2010	High	None	NA	HU	Ischemic stroke	Hypertension, dyslipidemia	670	Ongoing (Day 869)

- 5 TEs in high-risk patients (i.e., >60 years old and/or prior history of TEs) were reported
  - No TEs occurred in low-risk patients
- There were no TEs reported during the rusfertide phase 2 hemochromatosis and β-thalassemia studies

BMI, body mass index (kg/m^2); CRT, cytoreductive therapy; HU, hydroxyurea; NA, not applicable; PV, polycythemia vera; TE, thrombotic event; Yrs, years.

Data cutoff: 17 October 2023

Cancer History and Second Malignancies Reported on Study

Case	Age/Sex	Race	Malignancy	Grade	Relation	Day	Medical History	Prior PV treatment	Patient Status
Patients With Prior History of Skin Cancer									
1	72/F	White	• SCC in situ	2	• Not related	50	• Melanoma and multiple SCC	• HU ongoing for 5 years prior to event onset	• Ongoing (128+ weeks on study)
2	64/M	White	• BCC • Malignant melanoma Stage I	2 2	• Not related • Not related	171 171	• Multiple BCC • Multiple BCC	• Ruxolitinib ongoing for 15 months prior to onset of first event	• Ongoing (128+ weeks on study)
3	64/M	White	• SCC in situ • AML	1 3	• Not related • Unlikely related	226 253	• Melanoma and BCC • Radioiodine treatment for thyroid cancer (2015)	• HU ongoing for ≈5 years prior to onset of events	• Discontinued (Day 259)
4	70/F	American Indian/Alaska Native	• SCC in situ • BCC	2 2	• Unlikely related • Unlikely related	307 814	• Multiple BCC and SCC	• Ruxolitinib for 11 months, stopped ≈1 year before event onset	• Ongoing (144+ weeks on study)
5	68/M	White	• BCC	2	• Unlikely related	798	• BCC	• HU ongoing for 6 years prior to event onset	• Ongoing (160+ weeks on study)
Patients With Preexisting Lesions Prior to Rusfertide Exposure									
6	55/M	White	• BCC	2	• Unlikely related	234	• Preexisting lesion (captured in medical history; diagnosed only after initiation of rusfertide)	• None	• Discontinued (Day 498)
7	51/M	White	• Malignant melanoma Stage Ia	2	• Possibly related	562	• Undiagnosed lesion in the same area present prior to rusfertide exposure; history of atypical moles	• None	• Ongoing (128+ weeks on study)
Patients with Prior History of Cancer									
8	57/F	White	• Lung cancer	3	• Not related	226	• Cervix carcinoma, COPD, history of tobacco use	• Ruxolitinib, HU	• Discontinued (Day 988)

- In REVIVE, 19 of 70 patients (27.1%) had a history of cancer prior to enrolling on study
  - Of these patients, 10 (14.3%) had a history of skin cancer

*Day, time from first dose of rusfertide to diagnosis of malignancy on study.
AML, acute myeloid leukemia; BCC, basal cell carcinoma; HU, hydroxyurea; PV, polycythemia vera; SCC, squamous cell carcinoma.

Data cutoff: 17 October 2023

Conclusions

- In REVIVE (NCT04057040), rusfertide added to therapeutic phlebotomy with or without cytoreductive therapy provided long-term durable control of hematocrit and decreased phlebotomy use
- Rusfertide resulted in improved and normalized serum ferritin levels through 2.5 years
- After rising by ≈30%, platelets remained stable over time with continued rusfertide therapy
- Rusfertide is well-tolerated and has a safety profile consisting mostly of Grade 1 or 2 injection site reactions
  - Approximately 75% of TEAEs were grade 1 or 2; fewer than 25% of patients had a grade 3 AE
  - Second malignancies were reported in 8 patients on study
    - Prior malignancies, prior lesions, and/or the patient's medical history may have contributed to the etiology of these second malignancies
  - TEs were reported in 5 patients
    - Most patients (85.7%; 12 of 14) who experienced a TE prior to study entry did not have a recurrent TE on study (all TEs occurred in high-risk patients – none occurred in low-risk patients)
- Long-term follow up for efficacy and safety will continue for patients in REVIVE Part 3 (OLE)

AE, adverse event; OLE, open label extension; PV, polycythemia vera; TE, thrombotic event; TEAEs, treatment-emergent adverse events.

Data cutoff: 17 October 2023

Phase 3 Study VERIFY (NCT05210790): Rusfertide vs Placebo in Patients With PV[1,2]

≈250 Patients with PV Are Being Randomized Globally[1]

Key Eligibility:[1-3]

- Age ≥18 years
- Meet revised 2016 WHO criteria for diagnosis of PV
- ≥3 phlebotomies due to inadequate HCT control in 28 weeks[a] before randomization OR ≥5 phlebotomies due to inadequate HCT control within 1 year prior to randomization

N=250

Part 1A: Double-Blind[1,2]

32 weeks (Weeks 0-32)

R 1:1

- **Placebo + ongoing therapy**
- **Rusfertide + ongoing therapy** *Starting dose: 20 mg SC Q1W*

CRT may be decreased or stopped but not increased

Part 1B: Open-Label[1,2]

20 weeks (Weeks 32-52)

Goal: Assess durability of responses through Week 52

Rusfertide + ongoing therapy

CRT may be decreased or stopped but not increased

Part 2: Open-Label[1,2]

104 weeks (Weeks 52-156)[c]

Goal: Assess long-term safety

Rusfertide + PV therapy

Dose of CRT may be changed or new CRT may be initiated

Key Endpoints:[1,4,5]

- Proportion of patients achieving response, defined as absence of phlebotomy eligibility[b] (Weeks 20-32)
- Mean number of phlebotomies (Weeks 0-32)

[a]Defined as 28 weeks in protocol amendment 3.1, but previously published as 6 months.[2,3] [b]Phlebotomy eligibility defined as confirmed HCT ≥45% that is ≥3% higher than baseline, or HCT ≥48%.[1]

CRT, cytoreductive therapy; **HCT**, hematocrit; **PV**, polycythemia vera; **Q1W**, once a week; **R**, randomized; **SC**, subcutaneous; **WHO**, World Health Organization.

1. ClinicalTrials.gov. NCT05210790. https://clinicaltrials.gov/ct2/show/NCT05210790 **2.** Verstovsek S, et al. 64th American Society of Hematology (ASH) Annual Meeting; December 2022. TiP poster presentation. **3.** Protagonist Therapeutics. Protocol Number: PTG-300-11, Protocol Amendment 3.1. July 25, 2023. **4.** Protagonist Therapeutics. Press release. Published March 22, 2021. https://feeds.issuerdirect.com/news-release.html?newsid=6535012005620858 **5.** EU Clinical Trials Register. 2021-004732-29. https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-004732-29/HU.

Data cutoff: 17 October 2023

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