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VERIFY, A Phase 3 Placebo-Controlled Study Investigating Rusfertide With Current Standard of Care Therapy in Patients With Polycythemia Vera

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on behalf of the VERIFY Investigators

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Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm driven by acquired *JAK2* mutations[1-3]
- PV is characterized by excessive production of red blood cells, which contributes to an increased risk of cardiovascular and thrombotic events
- Primary goal of PV treatment aims to reduce thrombotic risk by achieving and maintaining Hct <45%[2,3]
- Current standard-of-care for PV: phlebotomy ± cytoreductive therapy
- Frequent phlebotomy is burdensome and often insufficient for durable Hct control <45%[4-6]

Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

1. Mora B, Passamonti F. *Clin Lymphoma Myeloma Leuk*. 2023;23(2):79-85; 2. Marchioli R, et al. *N Engl J Med*. 2013;368(1):22-33; 3. Tremblay D, et al. *JAMA*. 2025;333(2):153-60; 4. Alvarez-Larrán A, et al. *Haematologica*. 2016;102(1):103-9; 5. Verstovsek S, et al. *Ann Hematol*. 2023;102(3):571-81. 6. Ginzburg YZ, *Leukemia*. 2018;32(10):2105-16.

Rusfertide in Polycythemia Vera (PV)

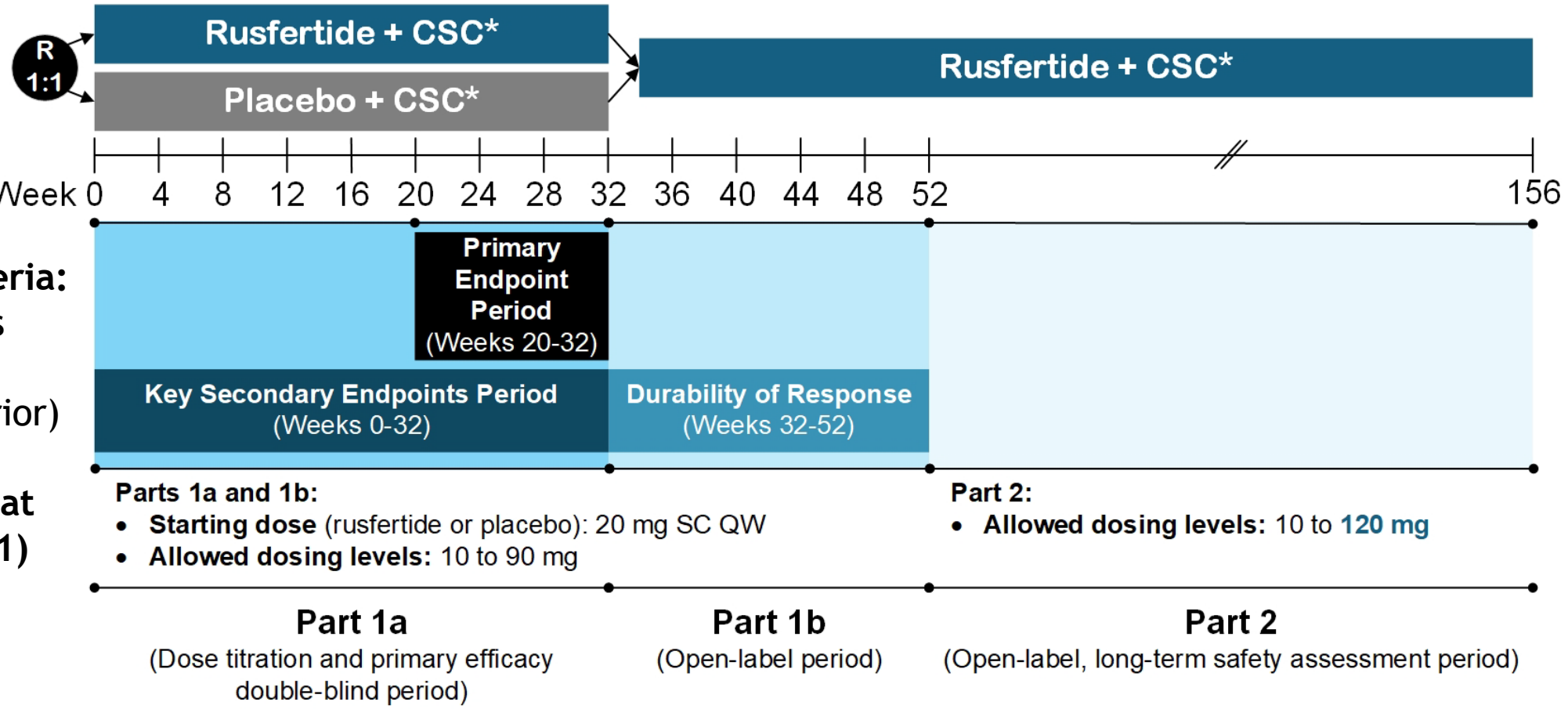
- Rusfertide is a first-in-class subcutaneous peptide mimetic of the endogenous hormone hepcidin, the principal regulator of iron homeostasis
- In the phase 2 REVIVE study (NCT04057040), rusfertide met the primary endpoint for response (ie, Hct control and absence of PHL eligibility) in patients with PV[1]
- VERIFY (NCT05210790) is a global, ongoing phase 3 study designed to confirm the benefit of rusfertide added to current standard-of-care (CSC) therapy vs placebo with CSC in patients with PV who require frequent PHLs

1. Kremyanskaya M, et al. *N Engl J Med*. 2024;390(8):723-35.
Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

Phase 3 VERIFY Study (NCT05210790) Design in PV

Key Inclusion Criteria:
- ≥3 PHL (28 weeks prior) OR
- ≥5 PHL (1 year prior)

Stratified by CSC* at randomization (1:1)



*PHL ± CRT

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera; QW, once-weekly; R, randomization; SC, subcutaneous.

Phase 3 VERIFY Study (NCT05210790) in PV

Prespecified Primary and Key Secondary Endpoints

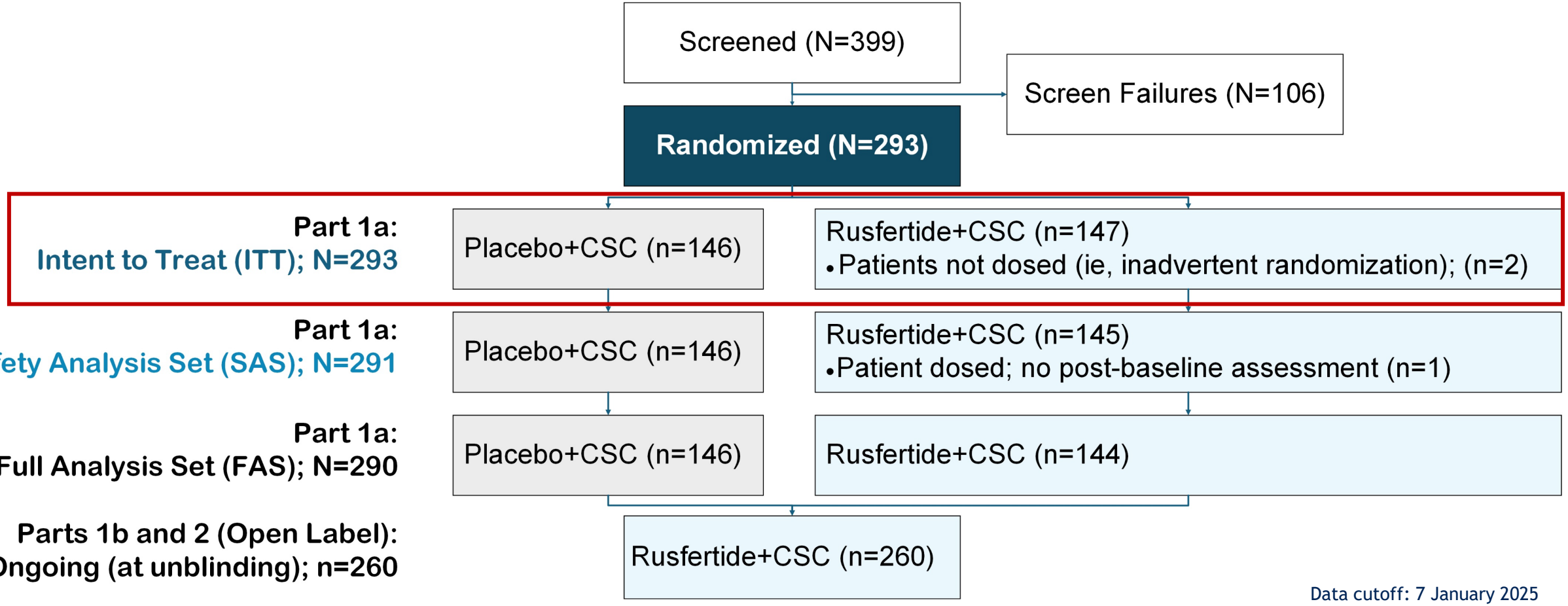
Rusfertide with CSC vs placebo with CSC:

- **Primary endpoint (US FDA):** Weeks 20-32
  - Clinical response (absence of phlebotomy eligibility, ie, confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%)

- **Key secondary endpoints:** Weeks 0-32
  - Mean number of phlebotomies (**EU EMA**)
  - Proportion of patients with Hct <45%
  - Mean change from baseline in PROMIS Fatigue SF-8a Score
  - Mean change from baseline in MFSAF TSS7

EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; Hct, hematocrit; MFSAF TSS, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score; PROMIS, Patient-Reported Outcomes Measurement Information System; PV, polycythemia vera; SF, short form.

VERIFY Patient Disposition and Analysis Sets: Part 1a



Data cutoff: 7 January 2025

FAS, all randomized patients according to the treatment assigned at randomization (ITT principle) who received at least one dose of study drug and had a baseline and at least one postbaseline assessment in Part 1a. CSC, current standard-of-care.

Baseline Demographics and Disease Characteristics

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)	Total (N=293)
Age, years, median (range)	57 (27-82)	58 (28-86)	57 (27-86)
Gender, n (%)			
Male	108 (74.0)	106 (72.1)	214 (73.0)
Female	38 (26.0)	41 (27.9)	79 (27.0)
Risk Category, n (%)			
High risk (age ≥60 years old and/or prior TE)	70 (47.9)	66 (44.9)	136 (46.4)
Disease Characteristics			
Age at PV diagnosis (years), median (range)	51 (22-81)	53 (17-84)	52 (17-84)
PV duration (years), median (range)	3 (0.2-29.2)	2.8 (0.2-26.4)	2.9 (0.2-29.2)
Phlebotomy History – 28 Weeks Prior to Study Treatment			
Number of TPs, mean ± SD	4.1 ± 1.4	4.2 ± 1.6	4.2 ± 1.5
Patients requiring ≥7 TPs, n (%)	7 (4.8)	16 (10.9)	23 (7.8)

Data cutoff: 7 January 2025

CSC, current standard-of-care; PV, polycythemia vera; SD, standard deviation; TE, thromboembolic event; TP, therapeutic phlebotomy.

Concurrent Cytoreductive Therapy During Part 1a

n (%)	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)	Total (N=293)
Patients With Concurrent Cytoreductive Medication	81 (55.5)	83 (56.5)	164 (56.0)
Hydroxyurea	57 (39.0)	58 (39.5)	115 (39.2)
Interferons			
Interferon, peginterferon alpha-2a, or ropeginterferon alfa-2b	20 (13.7)	19 (12.9)	39 (13.3)
JAK1/JAK2 Inhibitor			
Ruxolitinib	3 (2.1)	5 (3.4)	8 (2.7)

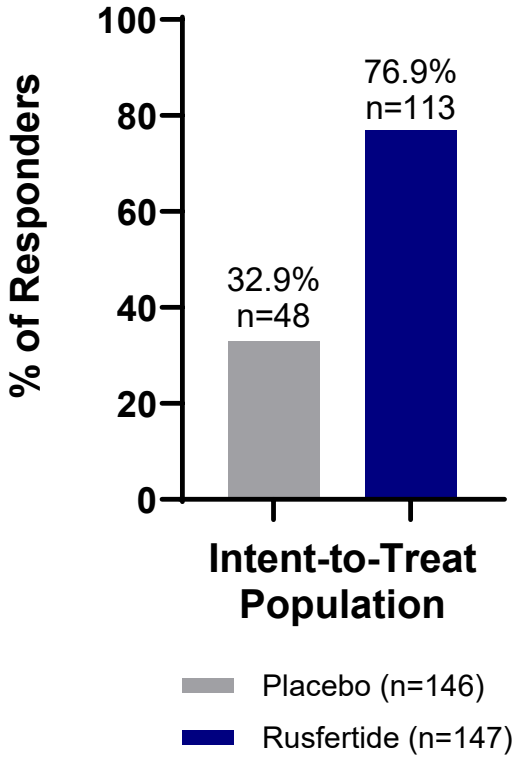
Data cutoff: 7 January 2025

CSC, current standard-of-care; JAK, Janus Kinase.

VERIFY Study Met Its Primary Endpoint During Weeks 20-32 (Part 1a)

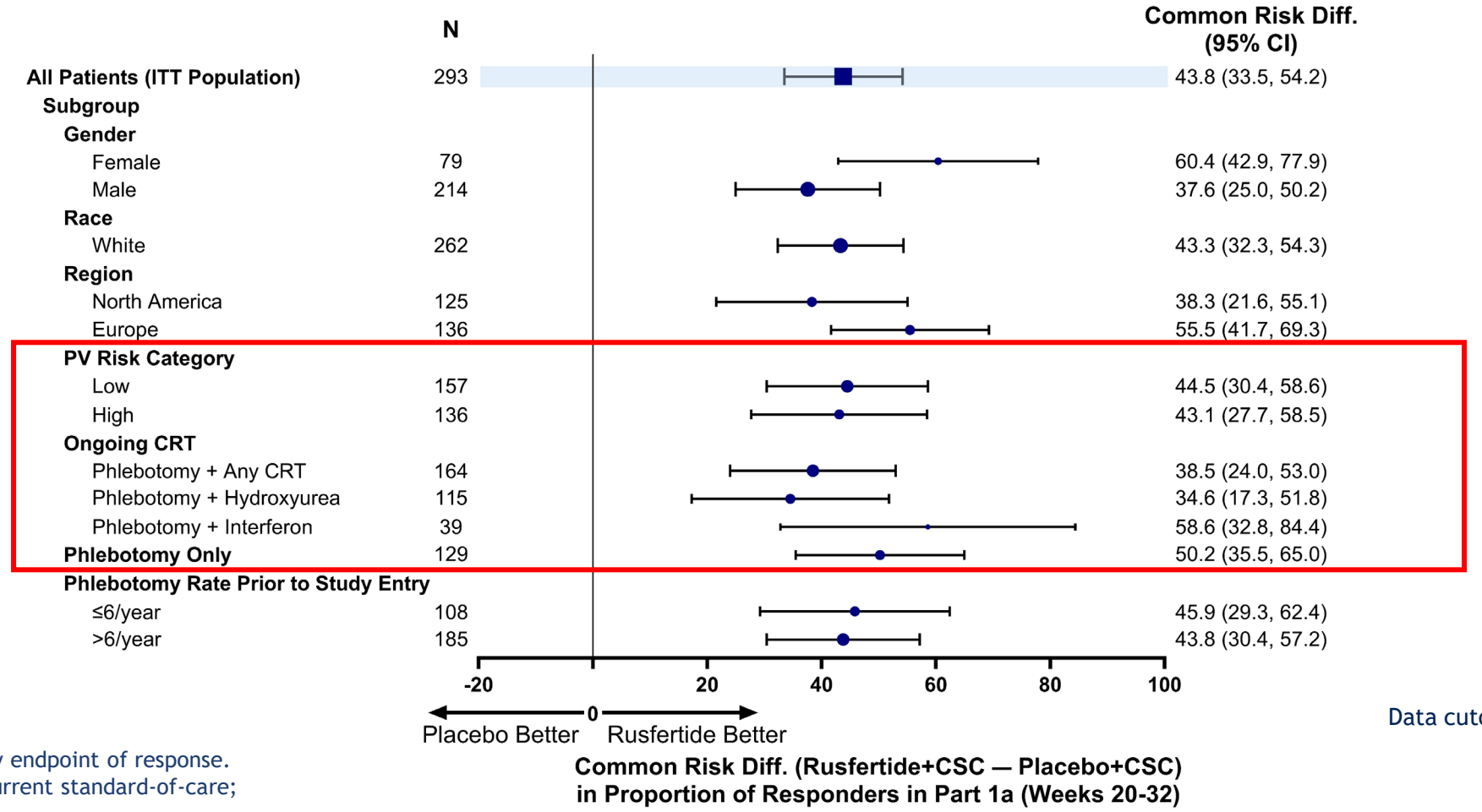
	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Responders, n (%)[a]	48 (32.9)	113 (76.9)
p-value*		<0.0001
Non-responders, n (%)	98 (67.1)	34 (23.1)

[a]Responder = absence of phlebotomy eligibility (confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%), no phlebotomies, and completion of Part 1a.
*p-value based on Cochran-Mantel-Haenszel test.
Hct, hematocrit.



Data cutoff: 7 January 2025

Rusfertide + CSC Benefit Maintained vs Placebo + CSC for Response* Across Subgroups, Including Risk Status and Concurrent Therapy



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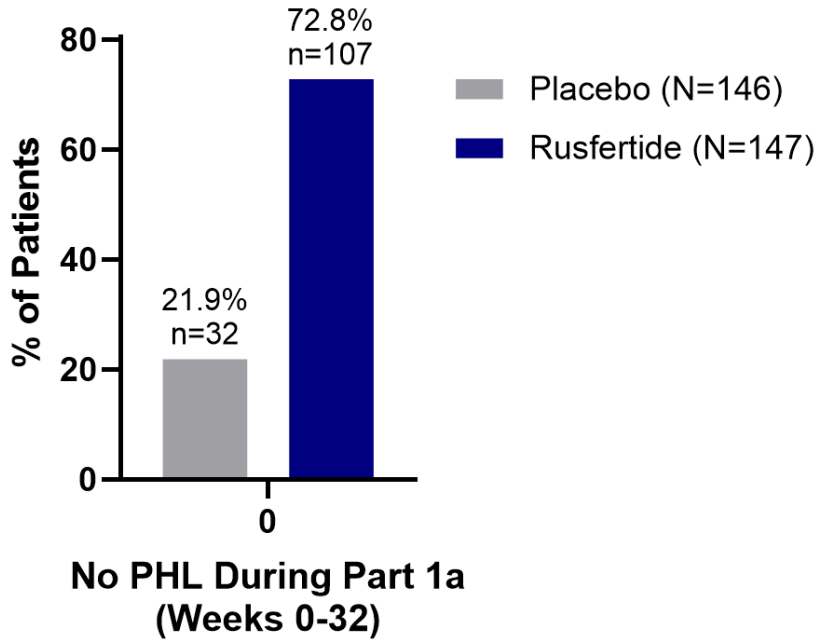
*Common risk difference for primary endpoint of response.
CRT, cytoreductive therapy; CSC, current standard-of-care; ITT, intent to treat.

Rusfertide + CSC Reduced the Mean Number of PHLs From Weeks 0-32 vs Placebo + CSC (p<0.0001): *Key Secondary Endpoint #1*

Number of Phlebotomies	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Mean (SD)	1.8 (1.5)	0.5 (1.2)
p-value*	<0.0001	

*p-value associated with the LS means difference.
LS, least-squares; SD, standard deviation.



- Rusfertide reduced the mean number of PHL (Weeks 0-32) vs placebo by a statistically significant margin across subgroups, including PV risk category, geographic region, and use of concurrent CRT

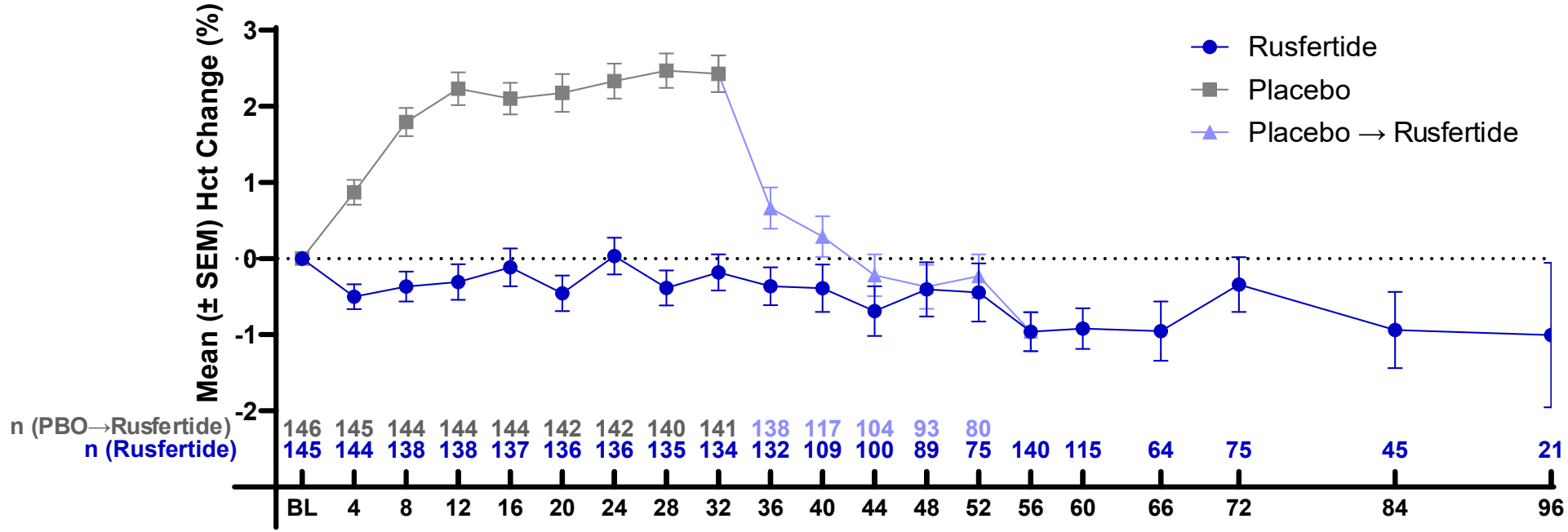
Data cutoff: 7 January 2025

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera.

Rusfertide + CSC More Likely to Maintain Hct <45% From Weeks 0-32 vs Placebo + CSC: *Key Secondary Endpoint #2*

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Hct <45% (Baseline through Week 32), n (%)[a]	21 (14.4)	92 (62.6)
p-value*		<0.0001

[a]Hct <45% from baseline through Week 32 (a single Hct ≥45% was allowed, excluding intercurrent events classified as non-responders).
*Cochran-Mantel-Haenszel test.

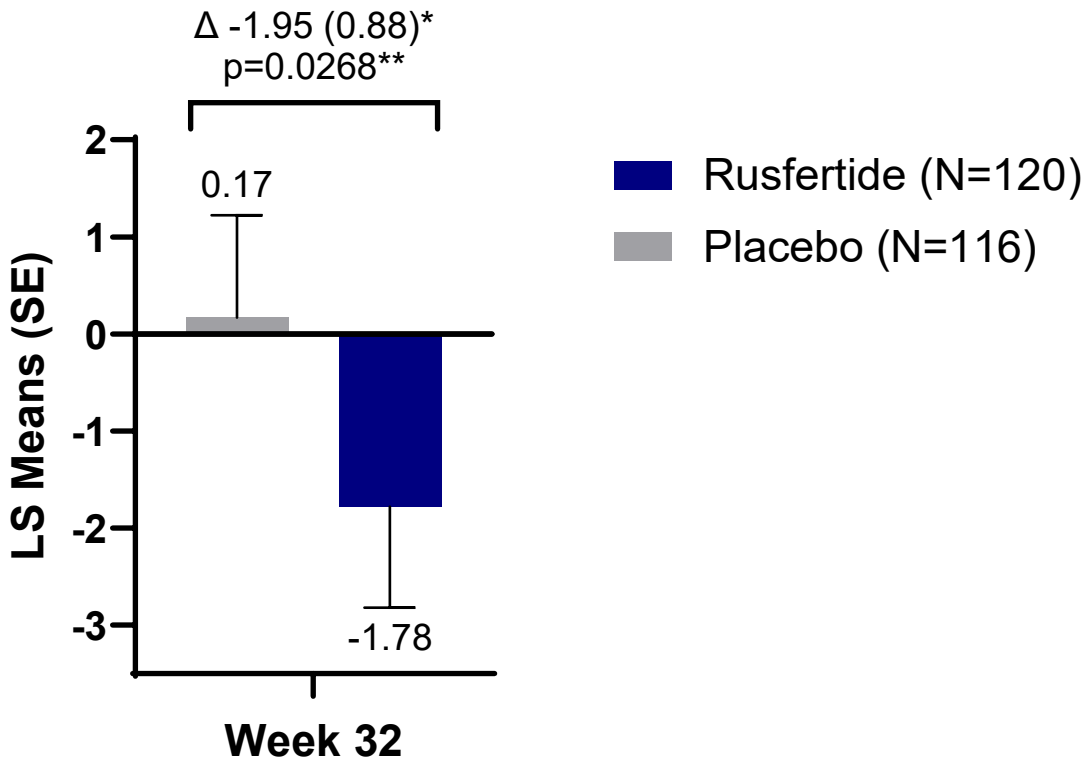


CSC, current standard-of-care; Hct, hematocrit; PBO, placebo; SEM, standard error of measurement.

Data cutoff: 7 January 2025

Rusfertide Demonstrated an Improvement in the PROMIS Fatigue SF-8a Total T-Score at Week 32 vs Placebo: *Key Secondary Endpoint #3*

LS Means Difference at Week 32:

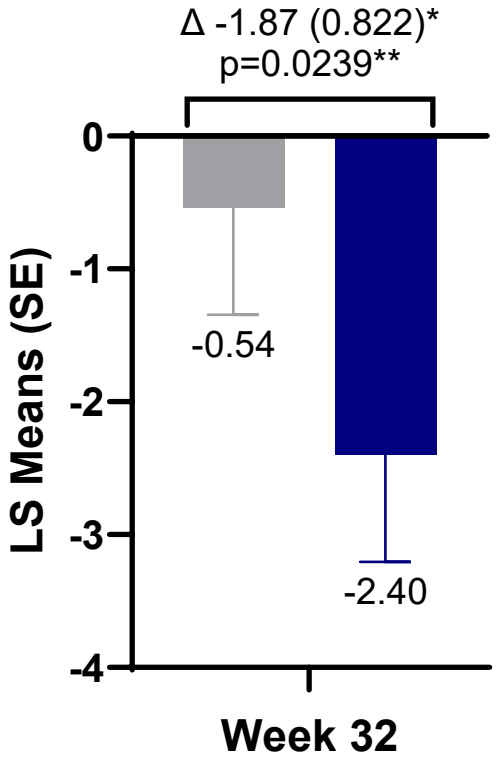


*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error; SF, short form.

Data cutoff: 7 January 2025

Rusfertide Demonstrated an Improvement in the MFSAF TSS7 at Week 32 vs. Placebo: *Key Secondary Endpoint #4*

LS Means Difference at Week 32:



Rusfertide (N=126)

Placebo (N=125)

- TSS7 includes fatigue, night sweats, itching, abdominal discomfort, pain under ribs on left side, early satiety, and bone pain

*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; MFSAF TSS7, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score-7 item; SE, standard error.

Data cutoff: 7 January 2025

Treatment-Emergent Adverse Events (Part 1a)*

- The most common TEAEs in the rusfertide group included localized injection site reactions and anemia
- Discontinuation rates due to TEAEs were 5.5% (rusfertide) and 2.7% (placebo)
  - Serious AEs occurred in 3.4% (rusfertide) and 4.8% (placebo) of patients (none related to rusfertide)
- There was 1 TE (acute MI; occurred ~2 weeks after treatment initiation) reported in the rusfertide group

Most Frequent TEAEs (≥6.5% in either group) in Part 1a, n (%)	Placebo + CSC (n=146)	Rusfertide + CSC (n=145)
Patients with at least 1 TEAE	126 (86.3)	129 (89)
Injection site reactions[a]	48 (32.9)	81 (55.9)
Anemia	6 (4.1)	23 (15.9)
Fatigue	23 (15.8)	22 (15.2)
Headache	17 (11.6)	15 (10.3)
COVID-19	16 (11.0)	14 (9.7)
Pruritus	14 (9.6)	14 (9.7)
Diarrhea	8 (5.5)	12 (8.3)
Dizziness	9 (6.2)	12 (8.3)
Arthralgia	12 (8.2)	11 (7.6)
Constipation	11 (7.5)	11 (7.6)
Abdominal distension	8 (5.5)	10 (6.9)

[a]Injection site reactions (grouped term); all other TEAEs are preferred terms.

Data cutoff: 7 January 2025

*Safety analysis set.

AE, adverse event; CSC, current standard-of-care; MI, myocardial infarction; TE, thromboembolic event; TEAE, treatment-emergent adverse event.

Conclusions

- Rusfertide is an investigational weekly subcutaneous injection for PV
- In the phase 3 VERIFY study that included patients with PV who were receiving CSC, rusfertide met its primary endpoint and all four key secondary endpoints vs placebo
  - In VERIFY Part 1a, rusfertide:
    - Significantly reduced PHL eligibility and maintained Hct continuously below 45% over the 32-week period
    - Significantly reduced the number of PHLs needed relative to placebo, with 72.8% of patients in the rusfertide arm not requiring a single PHL in the evaluation period
    - Demonstrated a statistically significant improvement in key symptoms impacting patients living with PV (assessed using two PRO instruments) vs placebo
- Rusfertide demonstrated a manageable safety profile consistent with prior studies
- **Rusfertide represents a potential new treatment option for PV**
  - These data will be used to file marketing authorizations throughout the world

CSC, current standard-of-care; Hct, hematocrit; PHL, phlebotomy; PRO, patient-reported outcome; PV, polycythemia vera.

We would like to thank all patients and their caregivers who participated in this study along with all investigators, study staff, and clinical trial sites who contributed to VERIFY

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