

Effect of Rusfertide on Cytooreductive Therapy Use in Patients with Phlebotomy Dependent Polycythemia Vera: Post Hoc Analysis from the Randomized Controlled Phase 3 VERIFY Study

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Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm that is characterized by the excessive production of erythrocytes and may include elevations in leukocytes and platelets^{1,2}
 - Over-proliferation of blood cells leads to elevated risk of thromboembolic events (TEs) and cardiovascular (CV) events
- Therapeutic phlebotomy is recommended for all patients with PV to control hematocrit (Hct) <45%, reduce the risk of arterial and venous TEs, and reduce CV mortality³⁻⁶
 - Use of phlebotomy with cytoreductive therapy (CRT) is recommended for patients with high-risk PV (defined as those ≥60 years old and/or those with a history of prior TEs) and uncontrolled Hct >45%
- Rusfertide is a first-in-class, subcutaneously injected peptide mimetic of hepcidin, the principal regulator of iron homeostasis⁷⁻⁸
- VERIFY (NCT05210790) is an ongoing phase 3 study that included patients with PV who were receiving frequent phlebotomy and had poorly controlled Hct⁹
 - During the randomized, placebo-controlled portion of the trial, rusfertide plus current standard-of-care (SOC) therapy met its prespecified primary endpoint of clinical response (absence of phlebotomy eligibility) and all four key secondary endpoints vs placebo with SOC¹⁰
 - The safety profile of rusfertide was consistent with prior phase 2 studies⁷⁻¹¹

Objective

- To describe dose increases, dose decreases, and treatment discontinuation of CRT in a post hoc analysis of VERIFY

Methods

- In the phase 3 VERIFY study, patients were randomized (1:1) to receive rusfertide or placebo with concurrent SOC therapy (ie, phlebotomy with or without CRT)
- After completing the 32-week double blind period, all patients were potentially eligible to receive rusfertide during the open-label period
- In this post hoc analysis, data from patients exposed to rusfertide (n=285) were analyzed to identify patients who:
 - Discontinued CRT without restarting CRT; or
 - Reduced their dose of CRT (ie, reduced weekly CRT dose [any magnitude] used at randomization and lasting ≥12 weeks without returning to their baseline weekly CRT dose); or
 - Increased their weekly CRT dose that was used at baseline or started a new CRT
- Results were analyzed using descriptive statistics

Results

- Baseline characteristics are summarized in **Table 1**
- These analyses included 293 randomized patients (rusfertide, n=147; placebo, n=146) with a median (range) age of 57 (27-86) years
 - Patients were 73.0% male, 46.8% had high-risk PV (rusfertide arm, 66/147 [44.9%]; placebo arm, 71/146 [48.6%]), and 55.3% were receiving concurrent CRT at baseline (rusfertide arm, 82/147 [55.8%]; placebo arm, 80/146 [54.8%])
- As of 10 December 2025, the median (range) duration of exposure for the 285 rusfertide-treated patients was 88.1 (2-158) weeks
 - At the cutoff date, 85% (242/285) of patients remained ongoing in VERIFY and continued to receive rusfertide with or without CRT

Table 1. Baseline Characteristics of VERIFY Patients

Characteristic	Part 1a (Baseline to Week 32)			Rusfertide-Treated Patients (n=285) ^a
	Rusfertide Arm (n=147)	Placebo Arm (n=146)	Randomized Patients (N=293)	
Age, median (range), years	58 (28-86)	57 (27-82)	57 (27-86)	57 (27-86)
Sex, n (%)				
Male	106 (72.1)	108 (74.0)	214 (73.0)	207 (72.6)
Female	41 (27.9)	38 (26.0)	79 (27.0)	78 (27.4)
Risk category, ^b n (%)				
High risk	66 (44.9)	71 (48.6)	137 (46.8)	129 (45.3)
Age only	49 (33.3)	43 (29.5)	92 (31.4)	88 (30.9)
TE only	5 (3.4)	15 (10.3)	20 (6.8)	19 (6.7)
Age and TE	12 (8.2)	13 (8.9)	25 (8.5)	22 (7.7)
Low risk	81 (55.1)	75 (51.4)	156 (53.2)	156 (54.7)
Phlebotomy + concurrent PV therapy, n (%)	82 (55.8)	80 (54.8)	162 (55.3)	156 (54.7)
Hydroxyurea	57 (38.8)	57 (39.0)	114 (38.9)	109 (38.2)
Interferon ^c	19 (12.9)	20 (13.7)	39 (13.3)	38 (13.3)
Ruxolitinib	5 (3.4)	2 (1.4)	7 (2.4)	7 (2.5)
>1 therapy	1 (0.7)	1 (0.7)	2 (0.7)	2 (0.7)
No concurrent PV therapy (phlebotomy alone), n (%)	65 (44.2)	66 (45.2)	131 (44.7)	129 (45.3)
PV, polycythemia vera; TE, thromboembolic events.				
^a Includes all patients treated with rusfertide in VERIFY (n=285). In VERIFY (N=293), 2 patients were randomized but not dosed; 6 patients (placebo group) discontinued treatment before receiving rusfertide. ^b High-risk is defined as age ≥60 years or a history of prior TEs. Low-risk is defined as age <60 years and no prior TEs. ^c Includes interferon, peginterferon alpha-2a, and ropeginterferon alfa-2b.				

REFERENCES

- Patel AB, et al. *Leuk Lymphoma*. 2024;1-13.
- Harrison CN, et al. *Nat Rev Dis Primers*. 2025;11(1):26.
- McMullin MF, et al. *Br J Haematol*. 2019;184(2):176-91.
- Marchetti M, et al. *Lancet Haematol*. 2022;9(4):e301-e11.
- Tefferi A, Barbui T. *Am J Hematol*. 2023;98(9):1465-87.
- Kuykendall AT, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24(8):512-22.
- Kremysavskaya M, et al. *N Engl J Med*. 2024;390(8):723-35.
- Cheng YZ. *Vitam Horm*. 2019;110:17-45.
- Protagonist Therapeutics, Inc. 2022. <https://clinicaltrials.gov/study/NCT05210790>.
- Kuykendall A, et al. *Blood*. 2025;146(Supplement 1):81.
- Chew LP, et al. *Leuk Res*. 2025;159:108132.

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Timing of weekly CRT dose reductions: hydroxyurea and interferon

- In rusfertide-treated patients who decreased their dose of CRT, the median (range) weekly dose of CRT in patients who received CRT concurrently at baseline was 7.0 g (2.5, 14.0) for hydroxyurea and 135.0 µg (15.0, 250.0) for interferon
 - In these patients, the median (range) time to first CRT reduction for hydroxyurea and interferon was 22.1 (2.0, 96.1) and 20.0 (2.1, 72.3) weeks, respectively
 - The median (range) percent change from baseline in weekly CRT dose at time of first CRT reduction was -40.8% (-5.9, -66.7) for hydroxyurea and -33.3% (-14.3, -50.0) for interferon
 - For patients with ≥1 CRT dose reduction, the median (range) time to last CRT reduction for hydroxyurea and interferon was 58.9 (9.0, 130.9) and 76.1 (6.1, 120.3) weeks, respectively
 - In these patients, the weekly dose of CRT at last reduction had a median (range) percentage change from baseline of -50.0% (-8.3, -84.6) for hydroxyurea and -62.5% (-42.9, -87.5) for interferon

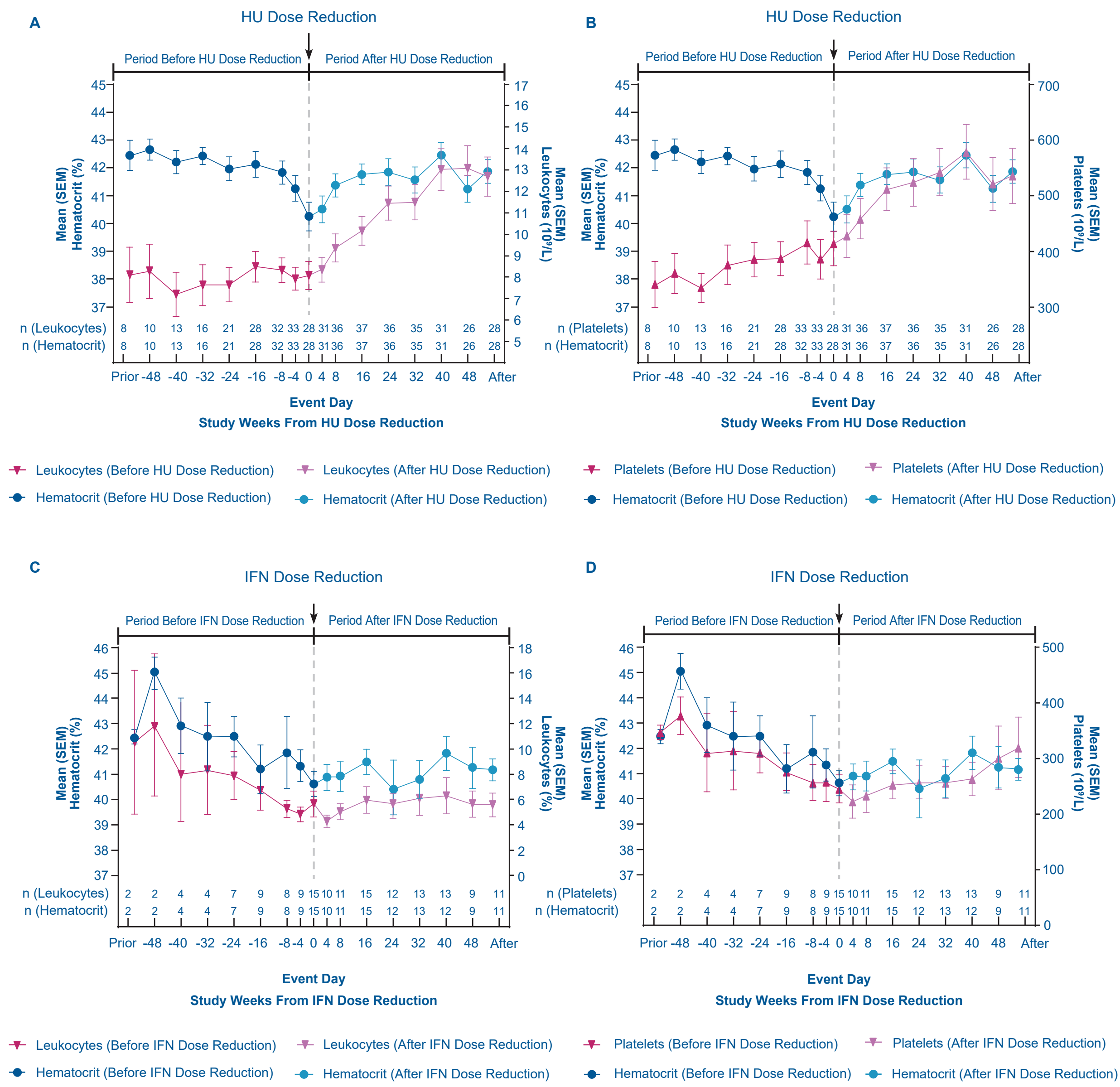
Change in Hct levels

- In rusfertide-treated patients who received phlebotomy plus hydroxyurea or interferon, mean Hct levels remained <45% irrespective of whether patients had a CRT dose reduction (**Figure 1**)
 - The annualized phlebotomy rate remained unchanged in these patients

Changes in leukocytes and platelets following CRT dose reduction or increase

- Leukocyte and platelet counts increased from baseline in rusfertide-treated patients who had a dose reduction in hydroxyurea (**Figure 1A, 1B**)
 - Larger proportional increases from baseline were observed in patients who discontinued hydroxyurea (data not shown)
- In rusfertide-treated patients who reduced their dose of interferon, leukocyte counts decreased slightly from baseline and stabilized throughout the course of the study; platelet counts remained below or similar to baseline levels (**Figure 1C, 1D**)
- In patients who were treated with concurrent hydroxyurea and had an increase in their CRT dose or started a new CRT, platelet counts remained similar to levels recorded prior to increases in CRT (data not shown)
 - In contrast, leukocyte counts decreased from baseline in patients treated with rusfertide and concurrent hydroxyurea who increased their CRT dose or started a new CRT
- Leukocyte and platelet counts declined slightly from baseline in patients who received concurrent interferon at baseline and who increased their CRT dose or started a new CRT (data not shown)

Figure 1. Changes in Hct and (A, C) WBCs and (B, D) Platelets in Patients Treated with Rusfertide Receiving Concurrent Treatment with (A, B) Hydroxyurea or (C, D) Interferon



CRT, cytooreductive therapy; Hct, hematocrit; WBC, white blood cell. Data on y-axes are mean (SEM). In Panels A-D, the "event" is dose reduction of CRT (HU, Panels A and B; IFN, Panels C and D). Numbers above the x-axes show the number of patients (n) for each time point (in weeks) before and after the event date at Week 0. Interferon includes interferon, peginterferon alpha-2a, and ropeginterferon alfa-2b.

Safety

- In the 90 days prior to change in CRT dose, treatment-emergent adverse events (TEAEs) occurred in 47/59 (79.7%) patients who reduced their CRT dose, 13/19 (68.4%) patients who discontinued CRT, and 30/39 (76.9%) patients who increased their CRT dose (**Table 4**)
 - In the same period, serious adverse events (SAEs) were reported by 1 patient in each group (CRT dose reduction: 1.7%; CRT discontinuation: 5.3%; CRT dose increase: 2.6%)
- The percentage of patients experiencing TEAEs in the 90 days following CRT dose reduction or discontinuation decreased in all groups (reduced CRT dose, 31/59 [52.5%]; discontinued CRT, 7/19 [36.8%]; increased CRT dose, 21/39 [53.8%]) (**Table 4**)
 - There were no SAEs in any group following CRT dose reduction, discontinuation, or increase
- In all groups, the majority of TEAEs were generally mild-to-moderate in severity following changes in CRT dose (**Table 4**)
- There were no discontinuations of rusfertide among those patients who reduced or discontinued CRT at any point in the study
 - Among patients who increased their baseline CRT dose, there were 2 rusfertide discontinuations (5.1%), 1 each in the 90 days prior to and the 90 days following dose increase
- There were no deaths in any of the groups at any point during the study

Table 4. Treatment-Emergent Adverse Events Before and After Change in CRT Dose

Patients, n (%)	All VERIFY (Parts 1a, 1b, 2, and 3)	
Reduced CRT Dose	90 days before CRT dose reduction (n=59)	90 days after CRT dose reduction (n=59)
Any TEAE	47 (79.7)	31 (52.5)
Grade 3 or 4 TEAEs	2 (3.4)	1 (1.7)
Any SAE	1 (1.7)	0
Discontinued CRT	90 days before CRT discontinuation (n=19)	90 days after CRT discontinuation (n=19)
Any TEAE	13 (68.4)	7 (36.8)
Grade 3 or 4 TEAEs	0	0
Any SAE	1 (5.3)	0
Increased CRT Dose	90 days before CRT increase (n=39)	90 days after CRT increase (n=39)
Any TEAE	30 (76.9)	21 (53.8)
Grade 3 or 4 TEAEs	2 (5.1)	0
Any SAE	1 (2.6)	0
CRT, cytooreductive therapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event.		

Conclusions

- In this post hoc analysis of the phase 3 VERIFY study, 41.7% of patients with phlebotomy-dependent PV who were treated with CRT at baseline discontinued or reduced their dose of CRT
 - After initiation of treatment with rusfertide, 12.2% of patients started a new CRT or increased their weekly CRT dose
- In rusfertide-treated patients who decreased their dose of CRT, median time to first CRT reduction in hydroxyurea and interferon dose occurred after 6.5 and 8.3 months, respectively
- After the final dose reduction of CRT, hydroxyurea and interferon were being administered at a median percentage change from baseline of -50.0% and -62.5%, respectively
- In patients who received rusfertide and reduced or discontinued their CRT dose, mean Hct levels remained <45% without an increase in their annualized phlebotomy rate to maintain Hct levels <45%
- CRT dose modifications or initiation of new CRT therapy did not have a marked effect on all-grade adverse events or SAEs in rusfertide-treated patients
- Taken together, these post hoc results suggest that rusfertide treatment provides rapid, durable, and sustained control of Hct levels and reduces phlebotomy burden in patients with PV, including in patients who undergo CRT dose reductions or CRT discontinuation

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