RESULTS FROM VERIFY, AN INTERNATIONAL, RANDOMIZED PHASE 3 DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF RUSFERTIDE (FIRST-IN-CLASS HEPCIDIN MIMETIC) FOR TREATMENT OF POLYCYTHEMIA VERA (PV)

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Introduction

- Polycythemia vera (PV) is characterized by excessive red blood cell production, which can increase the risk of cardiovascular and thrombotic events (TEs)[1-3]
- Guidelines recommend maintaining hematocrit (Hct) <45% to reduce the risk of TEs[2,3]
  - The current standard-of-care (CSC) for PV is phlebotomy (PHL) ± cytoreductive therapy (CRT)[3-5]
- Frequent PHL is burdensome and often insufficient for durable Hct control[6]
- Rusfertide is a first-in-class, self-administered subcutaneous peptide mimetic of the endogenous hormone hepcidin, the principal regulator of iron homeostasis[6-8]
- In the phase 2 REVIVE study (NCT04057040), rusfertide was superior to placebo in achieving and maintaining Hct <45% and reducing or eliminating the need for PHL in patients with PHL-dependent PV[8]
- VERIFY (NCT05210790) is a global, ongoing phase 3 study evaluating rusfertide added to CSC therapy vs placebo with CSC in patients with PV who require frequent PHLs[9,10]

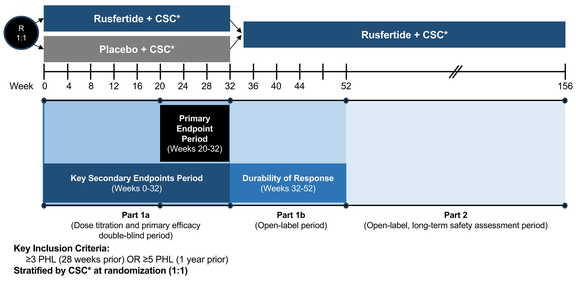
Objective

- To assess the efficacy and safety of subcutaneous rusfertide vs placebo in PHL-dependent patients with PV who were receiving CSC therapy prior to randomization

Methods

- In VERIFY Part 1a, patients requiring frequent PHL with or without CRT to achieve and maintain Hct <45% were randomized to receive once-weekly rusfertide or placebo (**Figure 1**)
  - All patients completing Part 1a received open-label rusfertide during Part 1b; patients completing Part 1b progressed to Part 2

Figure 1. VERIFY Study Design



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.

- Rusfertide with CSC vs placebo with CSC:
  - Primary endpoint (US FDA): Weeks 20-32
    - Clinical response (absence of PHL eligibility, ie, confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%)
  - Key secondary endpoints: Weeks 0-32
    - Mean number of PHLs (EU EMA)
    - Proportion of patients with Hct <45%
    - Mean change from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short-form (SF)-8a Score
    - Mean change from baseline in Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score-7 item (MFSAF TSS7)
- All patients provided informed consent

Results

- We randomized 293 patients to rusfertide (n=147) or placebo (n=146) (**Table 1**)
- Data cutoff was January 7, 2025

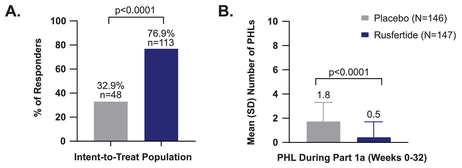
Table 1. Baseline Demographics and Disease Characteristics

	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)
PHL 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)

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

- During Part 1a, 56.5% (n=83) and 55.5% (n=81) of rusfertide- and placebo-treated patients, respectively, received concurrent CRT
- Median (min, max) dose was 30 (10, 90) mg in the rusfertide group
- Significantly more patients (a) achieved clinical response (**Figure 2A**) and (b) had fewer PHLs (**Figure 2B**) with rusfertide vs placebo (both endpoints p<0.0001)
- In the rusfertide group, 72.8% of patients were PHL-free (ie, no PHLs in Part 1a) vs 21.9% of patients in the placebo group
- Rusfertide + CSC maintained benefit vs placebo + CSC for response across subgroups, including risk status and concurrent therapy (**Figure 3**)

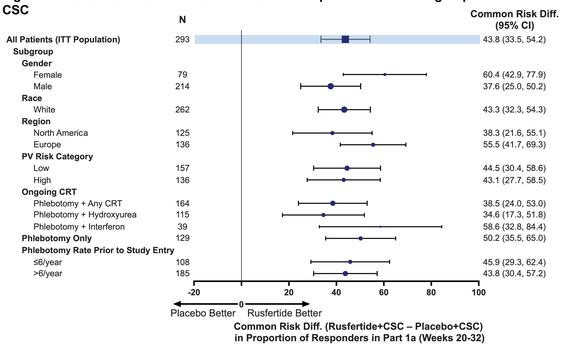
Figure 2. A) Primary Endpoint During Weeks 20-32 and B) Mean Number of PHLs During Weeks 0-32 (Key Secondary Endpoint #1)



Responders are defined as absence of PHL eligibility, ie, confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%. PHL, phlebotomy.

Results

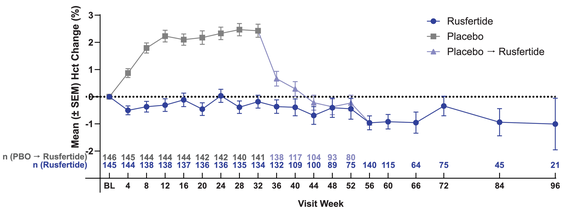
Figure 3. Rusfertide + CSC Maintained Benefit to Response* Across Subgroups vs Placebo + CSC



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

- Rusfertide + CSC was more likely to maintain Hct <45% from Weeks 0-32 (62.6%) vs placebo + CSC (14.4%) (p<0.0001)

Figure 4. Hct Remained Well Controlled in the Rusfertide Group



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

- Rusfertide-treated patients had statistically significant improvements in the PROMIS Fatigue SF-8a total T-score and MFSAF TSS7 vs placebo (p<0.03)
  - TSS7 includes fatigue, night sweats, itching, abdominal discomfort, pain under ribs on left side, early satiety, and bone pain
- The most common treatment-emergent adverse events (TEAEs) during Part 1a are reported in **Table 2**
  - Discontinuation rates due to TEAEs were 2.7% (placebo) and 5.5% (rusfertide)

Table 2. Most Frequent TEAEs (≥6.5% in Either Group) in Part 1a in the Safety Analysis Set

	Placebo + CSC n (%) (n=146)	Rusfertide + CSC n (%) (n=145)
Patients with at least 1 TEAE	126 (86.3)	129 (89)
Injection site reactions[a,b]	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)
Thrombocytosis	0	10 (6.9)
Pain in extremity	10 (6.8)	8 (5.5)

[a]Injection site reactions (grouped term); all other TEAEs are preferred terms.
[b]Most <grade 2.
AE, adverse event; CSC, current standard-of-care; TEAE, treatment-emergent adverse event.

- Serious AEs occurred in 3.4% (rusfertide) and 4.8% (placebo) of patients; none were treatment-related
- There was 1 thromboembolic event (acute myocardial infarction, which occurred approximately 2 weeks after treatment initiation) reported in the rusfertide group
- In total, 10 skin malignancies (including 1 melanoma) were detected prior to randomization
- During Part 1a, new malignancies occurred in <5% of patients in both groups combined
  - Malignancies were more frequent in the placebo arm

Conclusions

- 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 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 patient-reported outcome instruments) vs placebo
- Rusfertide demonstrated a manageable safety profile consistent with prior studies
- Rusfertide, a hepcidin mimetic, represents a novel therapeutic strategy to help patients with PV achieve Hct control and reduce the need for therapeutic PHL
  - These data will be used to file marketing authorizations throughout the world

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Author Disclosures can be found at: http://bit.ly/44RriAo

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