RUSFERTIDE (PTG-300) TREATMENT INTERRUPTION REVERSES HEMATOLOGICAL GAINS AND UPON REINITIATION, RESTORATION OF CLINICAL BENEFIT IS OBSERVED IN PATIENTS WITH POLYCYTHEMIA VERA

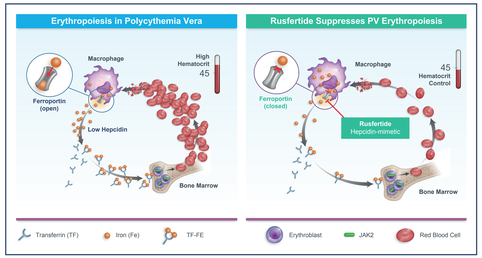
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Background

- Polycythemia vera (PV) is characterized by excessive red blood cell production and is associated with an increased risk of mortality due to thrombotic events when HCT levels are not controlled at <45%[1]
- PV is generally not optimally managed in most clinical settings[2]
  - In a 2-year period, only 22% of patients had HCT <45% on all tests; 49% had HCT >50% at least once[2]
  - Phlebotomy and cytoreductive therapies (e.g., hydroxyurea, ruxolitinib, and interferons) are not uniformly effective or tolerable
- PV is associated with suppression of hepcidin, in part, due to erythroid hyperplasia and iron deficiency[3]
- Rusfertide, a hepcidin mimetic, is being developed for patients with PV and uncontrolled erythrocytosis despite standard therapy
  - Rusfertide targets the ferroportin receptor in macrophages, and like hepcidin, rusfertide induces the endocytosis and proteolysis of ferroportin (**Figure 1**)
  - This leads to a decrease in the efflux of iron from this cellular site of iron storage, thus restricting iron availability for erythropoiesis

Figure 1. Rationale for Using Rusfertide in PV

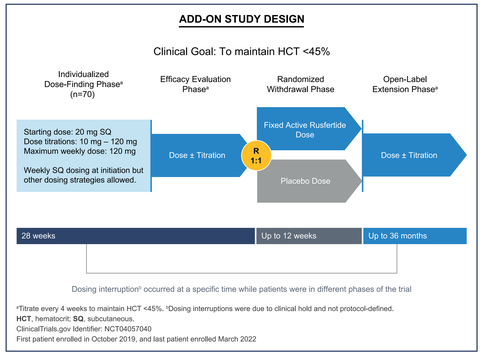


- Here, we report results from REVIVE (NCT04057040), a phase 2 clinical trial investigating rusfertide + therapeutic phlebotomy ± cytoreductive therapy in patients with phlebotomy-dependent PV

Methods

- REVIVE is a phase 2 clinical trial investigating rusfertide + therapeutic phlebotomy ± cytoreductive therapy in patients with phlebotomy-dependent PV diagnosed per 2016 WHO criteria
  - To be eligible, patients had to have had ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
  - All patients prior to first rusfertide dose were phlebotomized to hematocrit (HCT) <45% to standardize the starting HCT
- This was a 3-part study (**Figure 2**):
  - Part 1: a 28-week, open-label, dose-escalation phase in which each patient's dose of rusfertide (added prior to standard therapy) was titrated to achieve a HCT <45%
  - Part 2: a 12-week, blinded, randomized, withdrawal phase in which patients were randomized 1:1 to continue rusfertide or receive placebo
  - Part 3: an open-label extension of up to 3 years

Figure 2. REVIVE Study Design



[a]Titrate every 4 weeks to maintain HCT <45%. [b]Dosing interruptions were due to clinical hold and not protocol-defined.
HCT, hematocrit; **SQ**, subcutaneous.
ClinicalTrials.gov Identifier: NCT04057040
First patient enrolled in October 2019, and last patient enrolled March 2022

- The primary outcome measure was the proportion of patients achieving a response during the withdrawal phase (Week 29 to Week 41)
  - Response was defined as maintaining HCT control in the absence of 'phlebotomy eligibility'
  - Phlebotomy eligibility was defined as any one of the following: HCT ≥45% that was ≥3% higher than the Week 29 pre-randomization HCT value; or HCT >48%; or an increase of ≥5% in HCT compared to the Week 29 pre-randomization HCT value
- Secondary outcome measures included the change in rate of phlebotomy events between Week 17 through Week 29 and between Week 1 through Week 29 compared to each patient's historical rate
- Other outcome measures reported here include changes in rate of phlebotomy events, HCT and ferritin levels, and platelet and leukocyte counts assessed before and after a brief suspension in rusfertide treatment due to a clinical hold (not protocol-defined)
- Safety was also summarized

Results

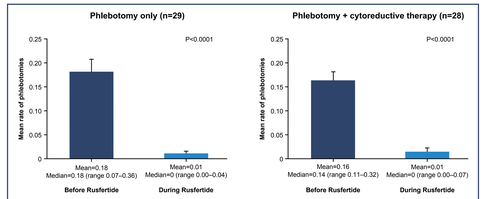
Phlebotomy rates before and during rusfertide treatment

- Rusfertide significantly decreased phlebotomy requirements in patients treated with phlebotomy only or cytoreductive therapy plus phlebotomy (**Figure 3**)
  - Number of phlebotomies in 28 weeks before treatment with rusfertide: mean 4.81 (median 4; range 2–10)
  - Number of phlebotomies after starting rusfertide: mean 0.30 (median 0; range 0–2)

Outcomes after rusfertide treatment interruption and reinitiation

- During a brief clinical hold on rusfertide clinical trials following nonclinical rasH2 mouse model findings, patients were maintained on their cytoreductive regimens and had therapeutic phlebotomy for HCT >45%
  - The study protocol was amended to add this information, dermatological screening, and stopping rules
  - Rusfertide was reinitiated following patient reconsent
- Most patients (85%) returned to rusfertide add-on treatment 2-3 months after the dosing interruption and reinitiation

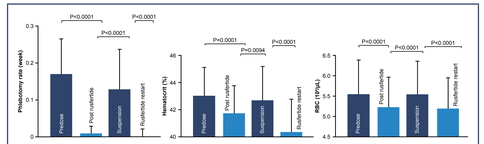
Figure 3. Mean Rate of Phlebotomies Before and During Part 1



Data cutoff: May 11, 2022.
Phlebotomy requirements are available for 57 patients who completed the first 28 weeks of dosing.
Error bars indicate 95% confidence intervals for the mean.

- Rusfertide treatment interruption led to loss of effect on phlebotomy rate, HCT, and red blood cells (RBC), and rusfertide restart restored the effect (**Figure 4**)

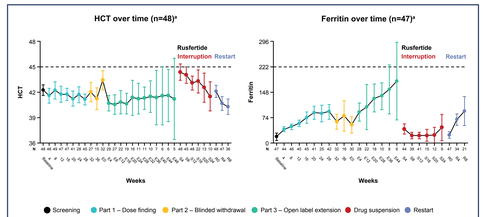
Figure 4. Clinical Effects of Rusfertide Treatment Interruption and Restart (n=48)[a]



Data cutoff: May 11, 2022
RBC, red blood cells
[a]Patients with complete restart data.

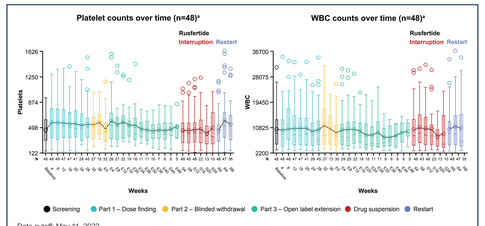
- Rusfertide treatment interruption also led to loss of effect on HCT and to decreased ferritin (**Figure 5**)
- A similar pattern was observed with RBC counts
- Rusfertide treatment interruption was associated with no clinically meaningful changes in platelet or leukocyte counts (**Figure 6**)

Figure 5. Effects of Rusfertide Treatment Interruption and Restart on HCT and Ferritin



Data cutoff: May 11, 2022
HCT, hematocrit
[a]Patients with complete restart data.

Figure 6. Effects of Rusfertide Treatment Interruption and Restart on Platelets and White Blood Cells



Data cutoff: May 11, 2022
WBC, white blood cells
[a]Patients with complete restart data.

- Reactive thrombocytosis may have resulted from localized iron deficiency[4]
  - Thrombocytosis was asymptomatic, stabilized over the course of treatment, and did not increase with higher rusfertide dose and treatment duration
  - Thrombocytosis was not associated with clinical sequelae

Safety

- Most treatment-emergent adverse events (TEAEs) were grade 1-2
- Injection site reactions (ISRs) were the most common TEAE and occurred in 80% of patients (**Table 1**)
  - All ISRs were transient, and no patient discontinued due to an ISR
- There were no grade 3 events related to rusfertide, and no grade 4 or 5 TEAEs
- There were 3 withdrawals due to TEAEs
  - 1 AML, 1 thrombocytosis (Grade 1), and 1 pulmonary embolism identified on study

Table 1: Treatment-Emergent Adverse Events

Any-grade TEAE in ≥10% (preferred term)	n (%)
Total number of patients	**70**
Injection site reaction	56 (80)
Fatigue	19 (27.1)
Pruritus	17 (24.3)
Arthralgia	16 (22.9)
Headache	15 (21.4)
Dizziness	13 (18.6)
Nausea	12 (17.1)
Anemia	11 (15.7)
Hyperhidrosis	9 (12.9)
Diarrhea	8 (11.4)
Insomnia	8 (11.4)
Dyspnea	8 (11.4)
COVID-19	7 (10)
Hyperuricemia	7 (10)
Pain in extremity	7 (10)

TEAE, treatment-emergent adverse event
Data cutoff: May 11, 2022

- Secondary malignancies
  - 5 patients (5.5%) had secondary malignancies (6 skin cancers [3 squamous cell carcinoma, 2 basal cell, 1 malignant melanoma], 1 acute myeloid leukemia [AML]) in all rusfertide-treated patients in phase 2 trials (N=90)
  - All skin cancers were in situ or stage 1, and patients with squamous cell cancers had previous skin cancers
  - All newly developed cancers were in patients with previous ruxolitinib and/or hydroxyurea treatment
  - The patient with AML had received prior radioactive iodine for thyroid cancer and was on hydroxyurea; the patient was 65 years of age at the time of AML diagnosis and had been on rusfertide for 251 days

Conclusions

- PV patients with erythrocytosis requiring frequent phlebotomy + cytoreductives were treated with rusfertide for up to 18 months
- Rusfertide therapy resulted in rapid, sustained, and durable HCT control without clinically meaningful increases in white blood cell numbers, platelet counts, or PV-related thromboses
  - Patients have been treated for up to 1.5 years and have remained 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 appears well tolerated with Grade 1-2 ISRs being the most frequent TEAE
  - The number of patients with secondary malignancy was consistent with previous reports in the PV population
- Rusfertide dosing was suspended due to a clinical hold and dosing was resumed subsequently
  - Treatment suspension led to loss of benefit (e.g., increased phlebotomy rate, increased HCT, decreased ferritin)
  - Rusfertide restart restored therapeutic benefits
- A phase 3 trial of rusfertide (VERIFY; NCT05210790) in patients with PV is currently underway

References

1. Marchioli R, et al. *N Engl J Med*. 2013;368:22–33.
2. Verstovsek S, et al. *Blood*. 2020;136(Supplement 1):Abstract 2998.
3. Ginzburg YZ, et al. *Leukemia*. 2018;32:2105–2116.
4. Kasper CK, et al. *JAMA*. 1965;191:359-363.

Acknowledgments

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Disclosures

Dr. Pemmaraju reports that he serves on the Board of Directors of Dan's House of Hope; provides consulting to AbbVie, Aptitude Health, Astellas Pharma US, Inc., Blueprint Medicines, Bristol-Myers Squibb, Celgene Corp, Cimeio Therapeutics AG, ClearView Healthcare Partners, CTI BioPharma, Dava Oncology, Immunogen, Incyte, Intellisphere, LLC, Novartis AG, Novartis Pharmaceuticals Corp, OncLive (Owned by Intellisphere, LLC), Patient Power, PharmaEssentia, Protagonist Therapeutics, Sanofi-aventis, Stemline Therapeutics, Inc., and Total CME; has a Financial Relationship (e.g. Stock, Royalty, Gift, Employment or Business Ownership) with Karger Publishers; has served as a Scientific/Advisory Committee Member for Cancer.Net, CareDx, CTI BioPharma, EUSA Pharma, Inc., Novartis Pharmaceuticals Corp, Pacylex, PharmaEssentia; and has served as Speaker/Preceptorship for AbbVie, Aplastic Anemia & MDS International Foundation, Curio Science LLC, Dava Oncology, Imedex, Magdalen Medical Publishing, Medscape, Neopharm, PeerView Institute for Medical Education, Physicians' Education Resource (PER), Postgraduate Institute for Medicine, and Stemline Therapeutics, Inc.
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