Updated Long-Term Results from the Phase 2 REVIVE Study Investigating the Hepcidin Mimetic Rusfertide in Polycythemia Vera Patients: Hematocrit Control and Therapeutic Phlebotomy Frequency

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Objective

To provide updated, long-term results from REVIVE, including data from patients who have received rusfertide for 3+ years

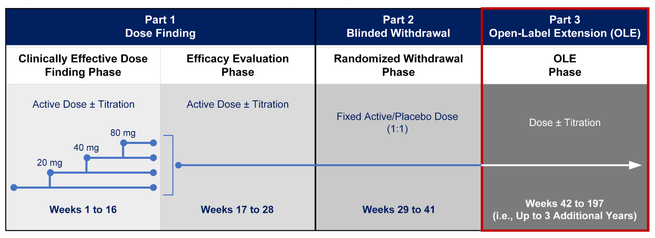
Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) that causes excess production of red blood cells; this condition can also increase leukocyte and platelet counts[1]
- Patients with PV have an increased risk of thrombosis due to elevated hematocrit (Hct) levels[2]
- Current treatments (eg, therapeutic phlebotomy and cytoreductive therapy) aim to reduce Hct <45%[3-6]
  - Therapeutic phlebotomy can cause iron deficiency, worsening PV symptoms such as fatigue;[2,7,8] phlebotomy can also be time consuming for both patients and their caregivers
    - Therefore, alternatives to therapeutic phlebotomy with or without cytoreductive therapy are needed[9]
- Rusfertide (PTG-300) is a weekly subcutaneous injectable peptide mimetic of the natural hormone hepcidin that restricts the availability of iron for RBC production[9-13]
- As reported previously, the phase 2 REVIVE study (PTG-300-04; NCT04057040) showed that rusfertide was superior to placebo in helping phlebotomy-dependent patients with PV achieve mean Hct levels <45% during a 12-week randomized withdrawal period (Part 2)[11,12] and provided long-term durable Hct control[13,14]

Methods

- In Part 1, subcutaneous rusfertide (starting dose: 20 mg Q1W) was initiated and titrated to control Hct to <45% (**Figure 1**)
- In Part 2 (Weeks 29-41; blinded randomized withdrawal phase), patients were randomized to receive rusfertide or placebo
- Randomized patients were eligible to participate in the open-label extension (OLE) portion of the study (Part 3), in which all patients received rusfertide and investigators could make CRT dose adjustments

Figure 1. Phase 2 REVIVE Study Design



OLE, open-label extension. Figure adapted from Pettit K, et al. Presented at EHA 2024, June 13-16, 2024, Madrid, Spain.[14]

Results

- As of April 9, 2024, 58 of 70 patients who enrolled in Part 1 had continued to Part 3 (OLE) (**Table 1**)
- Part 2 (n=59) was the randomized withdrawal phase; these data were reported previously[11,12]
- Overall, median (range) patient age was 58 (27-77); the majority were male (70%) and had high-risk disease (57.1%)
  - In Part 3, 55.2% and 44.8% of patients were treated with therapeutic phlebotomy alone or therapeutic phlebotomy with cytoreductive therapy, respectively

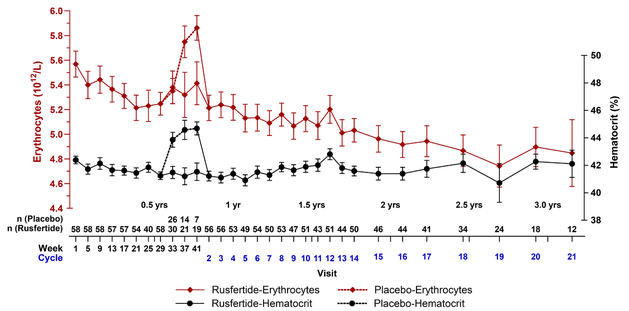
Table 1. Demographics and Disease Characteristics

	Part 1	Part 3
	Rusfertide N=70	Rusfertide N=58
Age, years, median (range)	58 (27-77)	57 (27-77)
Gender, n (%)		
Male	49 (70.0)	41 (70.7)
Female	21 (30.0)	17 (29.3)
Risk category, n (%)		
High risk	40 (57.1)	30 (51.7)
Low risk	30 (42.9)	28 (48.3)
Disease characteristics		
Age at PV diagnosis, years, median (range)	55 (5-74)	55 (26-74)
PV duration, years, median (range)	2.5 (0-35)	2.3 (0-22)
Phlebotomy history – 28 weeks prior to rusfertide treatment		
Number of phlebotomies, mean ± SD	4.7 ± 1.6	4.7 ± 1.6
Requiring ≥5 phlebotomies, n (%)	30 (42.9)	26 (44.8)
Concurrent therapy, n (%)		
Phlebotomy only	37 (52.9)	32 (55.2)
Phlebotomy + Cytoreductive therapy	33 (47.1)	26 (44.8)

PV, polycythemia vera; SD, standard deviation.

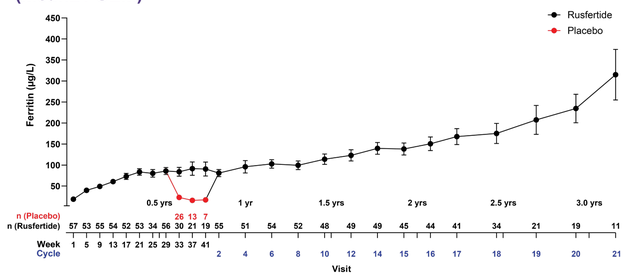
- In Part 3, the median weekly average dose of rusfertide was 40.6 mg (range, 5-95)
- Overall, median duration of exposure to rusfertide was 124.3 weeks (range, 3-205)
  - 48 patients (68.6%) have received rusfertide for ≥2 years
- Prior to enrollment, the estimated average (mean) phlebotomy rate (PHLR) in patients who enrolled on study was 8.7/year, which was reduced to <1.0/year in Part 1
  - In Part 2, the PHLR was <1.0/year and 6.0/year in the rusfertide and placebo groups, respectively
  - For patients who continued to Part 3 and received rusfertide, the PHLR remained at <1.0/year
- Starting within 4 weeks of treatment initiation, rusfertide consistently maintained Hct <45% in phlebotomy-dependent patients, including those who were on therapy for 3+ years (**Figure 2**)
  - Erythrocyte counts decreased and stabilized over time
- Rusfertide increased serum ferritin levels over time (**Figure 3**)
- Platelets increased post-baseline without significant clinical sequelae and stabilized over time (**Figure 4**)
  - Mean leukocyte counts remained stable throughout the study
- The most common (≥20%) TEAEs were injection site reactions, fatigue, COVID-19, pruritus, arthralgia, dizziness, nausea, anemia, and headache (**Table 2**)
  - Grade 3 TEAEs occurred in 25.7% of patients
  - There were no Grade 4 or 5 TEAEs
- Overall, 15 patients (21.4%) experienced serious adverse events (SAEs)
  - Most SAEs were unrelated and likely associated with the underlying disease
  - 1 SAE was assessed as treatment related by the investigator
- On study, there were 6 thrombotic events (TEs) that occurred in 5 patients
  - All 5 patients had high-risk disease (2 patients had a TE prior to study entry)
    - One patient with portal vein thrombosis prior to study entry had a myocardial infarction (MI) (Part 1, Week 10) and developed a recurrent MI (Part 3, Week 95); this patient remains on study (Week 108+)

Figure 2. REVIVE Parts 1-3: Erythrocytes and Mean Hematocrit (%)



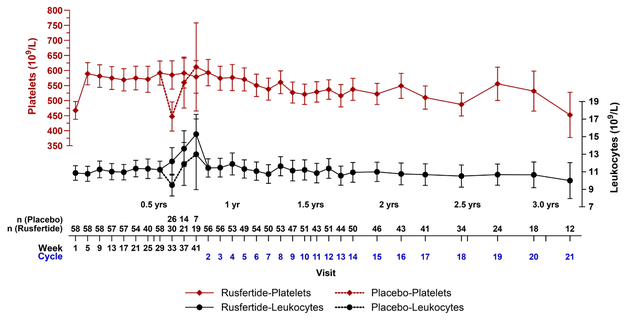
yr, year.

Figure 3. REVIVE Parts 1-3: Serum Ferritin (Central) Data (Mean±1 SEM)



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

Figure 4. REVIVE Parts 1-3: Platelets and Leukocytes (Mean±1 SEM)



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

Table 2. TEAEs (Any Grade) Reported in ≥10 Patients

	Overall, n (%)
Patients with at least 1 TEAE	70 (100.0)
Injection site erythema	46 (65.7)
Injection site pain	30 (42.9)
Injection site pruritus	27 (38.6)
Fatigue	25 (35.7)
COVID-19	22 (31.4)
Injection site mass	21 (30.0)
Pruritus	21 (30.0)
Arthralgia	19 (27.1)
Dizziness	19 (27.1)
Injection site swelling	17 (24.3)
Nausea	17 (24.3)
Anemia	16 (22.9)
Headache	16 (22.9)
Injection site irritation	14 (20.0)
Diarrhea	12 (17.1)
Injection site bruising	11 (15.7)
Dyspnea	10 (14.3)
Hyperhidrosis	10 (14.3)
Injection site warmth	10 (14.3)
Myalgia	10 (14.3)
Paresthesia	10 (14.3)
Upper respiratory tract infection	10 (14.3)

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

- In total, 11 of 70 patients (15.7%) reported a malignancy on study
  - Skin malignancies were identified in 9 patients on study
  - There was no apparent increase in malignancies on study with increasing exposure to rusfertide

Conclusions

- In REVIVE, rusfertide added to phlebotomy with or without cytoreductive therapy in patients with PV who were dependent on phlebotomy prior to study entry provided long-term durable control of Hct
- Changes in platelets were asymptomatic and stabilized over time
- Rusfertide was well-tolerated; the most common TEAEs were injection site reactions
  - Grade 3 TEAEs occurred in 25.7% of patients; there were no Grade 4 or 5 TEAEs
  - Non-PV malignancies were reported in 11 patients
  - 6 TEs were reported in 5 patients with high-risk PV
    - No TEs were reported in patients with low-risk PV
- Patients in Part 3 of REVIVE (OLE) are eligible to roll over to the phase 2 THRIVE OLE study (NCT06033586) to continue receiving rusfertide for up to 2 years, ie, a total of 5.8 years of rusfertide therapy[15]
  - As of April 27, 2024, of the 58 patients who enrolled in the OLE portion of REVIVE, 47 patients (81.0%) remain on rusfertide therapy
- The randomized phase 3 VERIFY study (NCT05210790) is evaluating rusfertide + phlebotomy ± cytoreductive therapy vs placebo + phlebotomy ± cytoreductive therapy in patients with PV and has reached its randomization target (~250 patients)[16]
  - Top-line data from VERIFY are anticipated during Q1 2025

DISCLOSURES

AG: consultancy role with AbbVie; **ATK:** honoraria from Incyte, PharmaEssentia, Protagonist Therapeutics; research funding from Novartis, Protagonist Therapeutics; **MK:** consultancy/advisory role with AbbVie, Agios, Constellation/MorphoSys, Disc Medicine, Incyte, Protagonist Therapeutics, Silence Therapeutics; **EKR:** consultancy/advisory role with Astellas Pharma, BMS, Incyte, Jazz Pharmaceuticals, Novartis, Pfizer; research funding from Astellas Pharma, BMS, Incyte, Jazz Pharmaceuticals, NS Pharma, Pfizer; speakers' bureau for Ariad, Incyte; travel expenses from Novartis, Pfizer; **JG, JP:** no relevant disclosures; **KMP:** consultancy/advisory role with AbbVie, Incyte, PharmaEssentia, Protagonist Therapeutics, Sierra oncology; research funding from AbbVie, Blueprint Medicines, BMS, Imago, Kura Oncology, Merck, Protagonist; **UKN:** no relevant disclosures; **AY:** consultancy/advisory role with AbbVie, ACCELERON PHARMA, Apellis, BMS, CTI Pharma, Gilead, Incyte, Notable Labs, Novartis, Pfizer, PharmaEssentia, Servier; **SG, SK, AM:** employment with Protagonist Therapeutics; **NP:** honoraria from AbbVie, Aptitude Health, Blueprints Medicines, Care DX, Celgene, DAVA Pharmaceuticals, Incyte, LFB Biotechnologies, Mustang Bio, Neo Pharm, Novartis, Roche Molecular Diagnostics, Springer Science + Business Media LLC, Stemline Therapeutics, Neo Pharm; consultancy/advisory role with Astellas Pharma US Inc., Blueprint Medicines, BMS, Clearview Healthcare Partners, CTI Bio Pharma Corp, Immunogen, Pacylex Pharmaceuticals Inc, Protagonist Therapeutics, Triptych Health Partners; research funding from AbbVie, Affymetrix/Thermo Fisher Scientific, Cellectis, Daiichi Sankyo, Mustang Bio, Novartis, Plexxikon, Samus Therapeutics, Stemline Therapeutics; travel expenses from AbbVie, Celgene, DAVA oncology, Mustang Bio, Stemline Therapeutics.

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