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VERIFY: A Randomized Controlled Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera (PV)

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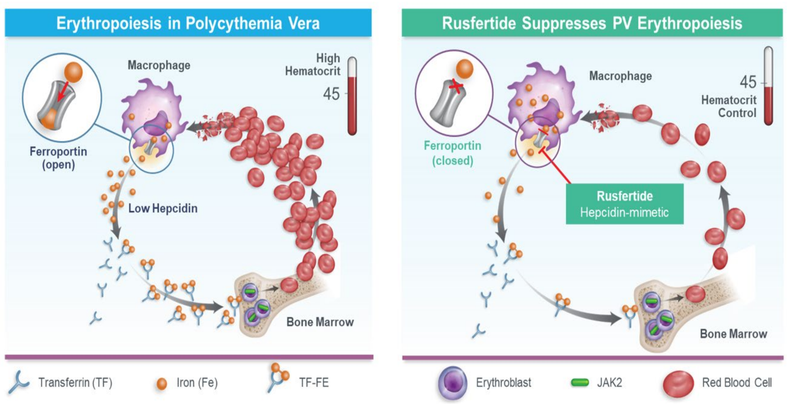
Objective

- To evaluate the safety and efficacy of rusfertide in maintaining hematocrit (Hct) control in patients with PV

Introduction

- Polycythemia vera (PV) is a myeloproliferative neoplasm (MPN) characterized by the overproduction of red blood cells[1]
  - Many patients with PV spend a significant amount of time with elevated Hct (>45%), increasing the risk of thrombosis[2]
  - In addition to erythrocytosis, many patients also experience other disease-related symptoms associated with PV, including pruritus, night sweats, difficulty concentrating, and fatigue[3,4]
- Current treatments for PV include aspirin, therapeutic phlebotomy, and cytoreductive therapies (eg, hydroxyurea, ruxolitinib, and interferon)[5-8]
  - Despite these options, many patients are at high risk of complications due to inadequate Hct control[8]
- Rusfertide (formerly known as PTG-300) is a peptide mimetic of the natural hormone hepcidin that restricts the availability of iron for red blood cell production (**Figure 1**)[9]

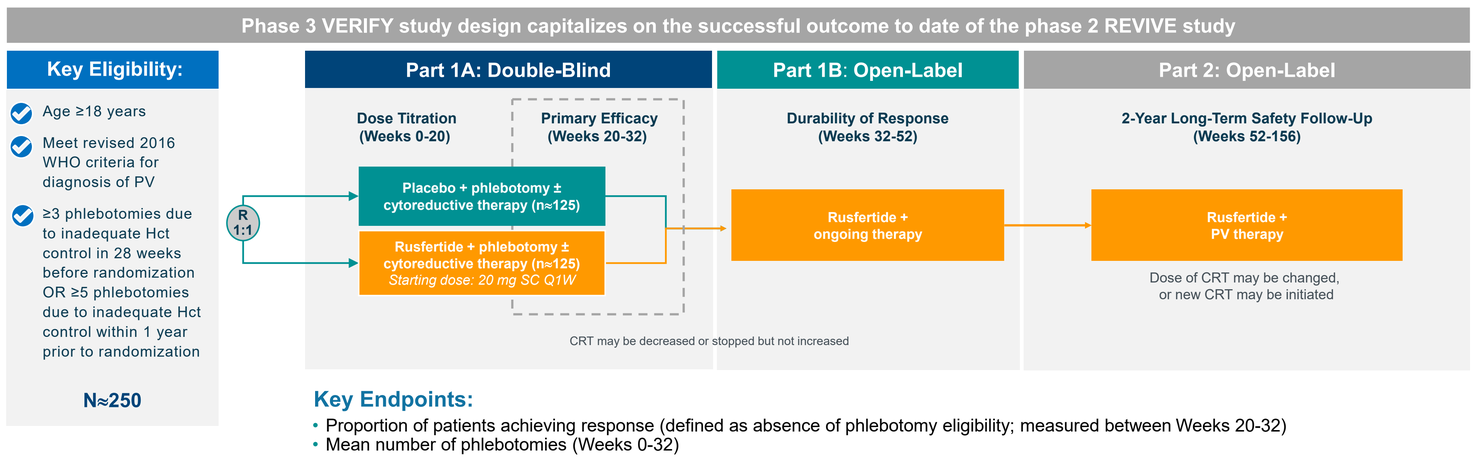
Figure 1. Rusfertide Mechanism of Action[10]



From Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients, presented by Ronald Hoffman at the 2021 ASH Annual Meeting. Reproduced with permission.
When serum levels of the natural hormone hepcidin are low, iron absorption and recycling proceed freely, which provides iron for erythropoiesis. It is hypothesized that patients with PV have relative suppression of hepcidin, which may occur because of iron deficiency and marrow erythroid hyperplasia, enabling sufficient availability of iron to support persistent erythrocytosis. Rusfertide restricts the availability of iron for red blood cell production, suppressing erythrocytosis.[11,12]
JAK2, Janus Kinase 2; PV, polycythemia vera.

- In the phase 2 REVIVE study (NCT04057040), rusfertide met the primary endpoint for response (patient defined as a responder if they had Hct control, did not undergo phlebotomy, and completed the 12-week trial regimen during Part 2 of the study)
  - In the full analysis population (n=53), response rates in the rusfertide and placebo groups were 69.2% and 18.5%, respectively, while in the randomized population (n=59), response rates were 60.0% (rusfertide group) and 17.0% (placebo group)[13-14]
  - Rusfertide was well-tolerated, with no Grade 4 or 5 treatment-emergent adverse events (TEAEs); the majority (77.1%) of TEAEs had a maximum grade of 2[9]
- The phase 3 VERIFY study (NCT05210790) aims to confirm and extend the findings from the phase 2 REVIVE study in patients with PV[15]

Figure 2. Trial Design



CRT, cytoreductive therapy; PV, polycythemia vera; R, randomized; SC, subcutaneous; Q1W, once weekly.

Methods

- The phase 3 VERIFY study is a multicenter, global randomized trial comparing rusfertide as a subcutaneous injection at a starting dose of 20 mg once weekly vs placebo when added to ongoing PV therapy
- The study population includes patients with PV who require frequent phlebotomies with or without concurrent cytoreductive therapy to control their Hct
- VERIFY is a three-part study (**Figure 2**):
  - Part 1a: 1:1 randomized, double-blind, placebo-controlled, add-on parallel-group period lasting 32 weeks (Week 0 to 32);
  - Part 1b: open-label treatment phase with cross-over for previous placebo-treated patients. During this phase of the study, all patients who complete Part 1a successfully will receive rusfertide for 20 weeks (Week 32 to 52); and
  - Part 2: long-term extension phase during which all patients who complete Part 1b will continue to receive rusfertide for 104 weeks (Week 52 to 156)

Key Eligibility Criteria

- Major inclusion criteria:
  - PV diagnosis (2016 World Health Organization criteria) defined as:
    - **Major criteria**: (1) Hemoglobin (Hgb) >16.5 g/dL (men) / Hgb >16.0 g/dL (women) **OR** Hct >49% (men) / Hct >48% (women) **OR** increased red cell mass; (2) Presence of JAK2 V617F or JAK2 exon 12 mutation; (3) Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size); however, bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis: Hgb >18.5 g/dL (men) / Hgb >16.5 g/dL (women) **OR** Hct >55.5% (men) / Hct >49.5% (women)
    - **Minor criteria:** Subnormal serum erythropoietin level
    - A PV diagnosis requires meeting all 3 major criteria or the first 2 major criteria and 1 minor criterion
  - Other major inclusion criteria:
    - Phlebotomy requiring, defined as ALL of the following: (1) ≥3 phlebotomies due to inadequate Hct control in 28 weeks before randomization **OR** ≥5 phlebotomies due to inadequate Hct control in 1 year before randomization; and (2) Last phlebotomy due to inadequate Hct control ≤3 months before randomization; and (3) No phlebotomy ≤6 days prior to randomization
    - Hct <45%, white blood cells 4-20 × 10^9/L and platelets 100-1000 × 10^9/L at Week 0 prior to randomization
    - Patients receiving cytoreductive therapy at randomization must be on a stable PV therapy regimen as follows: Hydroxyurea ≥2 months; JAK inhibitor ≥2 months; Interferon ≥6 months
    - Patients treated with phlebotomy alone at randomization must have stopped cytoreductive therapy as follows: Hydroxyurea ≥2 months before screening; JAK inhibitor ≥2 months before screening; Interferon ≥6 months before screening
- Major exclusion criteria:
  - Thrombosis or bleeding (active and/or chronic) deemed clinically significant by the investigator within 2 months before randomization
  - History of invasive malignancies within the last 5 years, except
    - Localized cured cancer (eg, prostate cancer and cervical cancer)
    - Localized cured in situ or stage 1 squamous cell carcinoma, basal cell carcinoma, or in situ melanoma of the skin
  - In situ or stage 1 squamous cell carcinoma of the skin, in situ or stage 1 basal cell carcinoma of the skin, or in situ melanoma of the skin identified during screening unless properly treated pre-randomization

Primary Endpoint

- Proportion of patients achieving response, defined as absence of phlebotomy eligibility (Weeks 20-32)
  - Phlebotomy eligibility defined as confirmed Hct ≥45% that is ≥3% higher than baseline **OR** Hct ≥48%

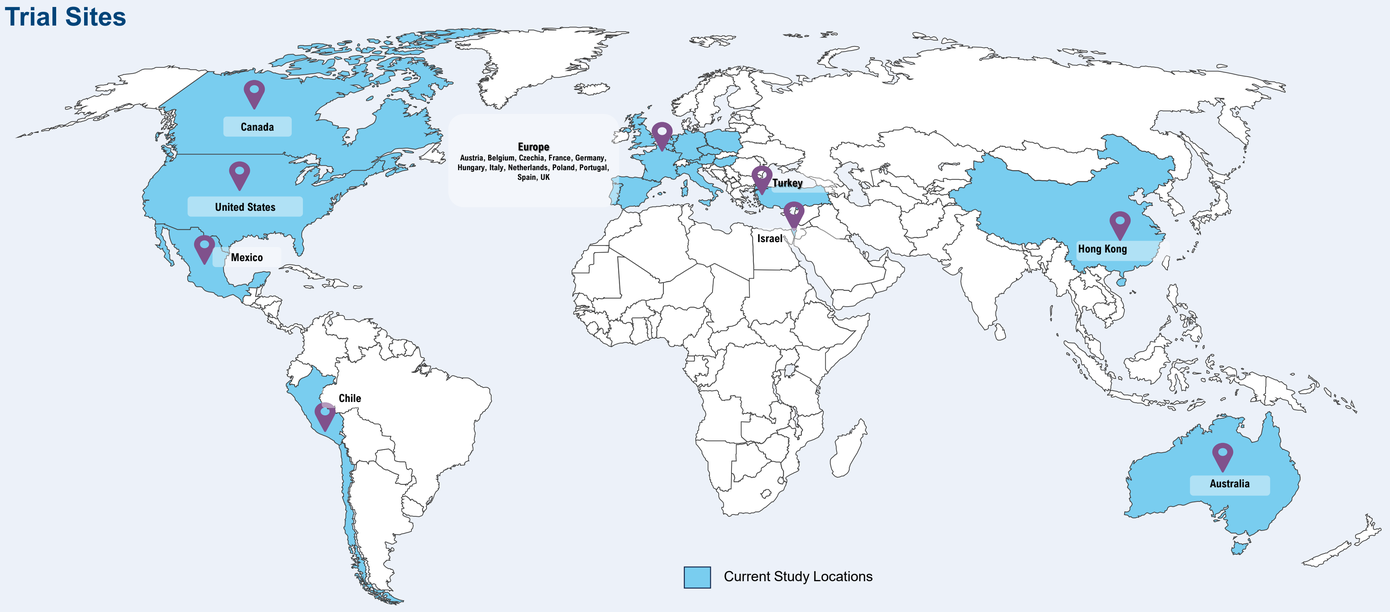
Key Secondary Endpoints: Weeks 0-32

- Mean number of phlebotomies
- Proportion of patients with Hct <45%
- Mean change from baseline in total fatigue score measured by Patient Reported Outcomes Measurement Information System (PROMIS) Short Form and in total symptom score measured by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0

Other Secondary Endpoints

- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) 10 at 32 weeks
- Mean change from baseline in the individual domain scores and the total EORTC QLQ-C30 score at 32 weeks
- Proportion of subjects originally randomized to rusfertide achieving absence of phlebotomy eligibility (durable response) for 52 weeks
- Median time to first confirmed Hct ≥45% during Part 1b excluding Part 1a
- Median time to first phlebotomy during Part 1b excluding Part 1a

Clinical Trial Sites



Conclusions

- VERIFY opened in January 2022 and achieved its randomization target of over 250 patients at over 100 clinical sites globally in April 2024[15]
- Top-line data for VERIFY's 32-week primary efficacy endpoint are expected by the end of the first quarter of 2025

2024 ASCO ANNUAL MEETING

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