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Thromboembolic and Progression Events in Phlebotomy-Dependent Patients with Polycythemia Vera (PV): Long-Term Results From the Phase 2 REVIVE and THRIVE Open-Label Extension Rusfertide Studies

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BACKGROUND

- Patients with polycythemia vera (PV) are at increased risk of morbidity and mortality due to disease progression or transformation, cardiovascular (CV) events, and thromboembolic events (TEs)[1-6]
- Rusfertide is a first-in-class, subcutaneously injected, self-administered peptide mimetic of the endogenous hormone hepcidin, the principal regulator of iron homeostasis[7-10]
- In the phase 2 REVIVE study (NCT04057040), rusfertide met the primary endpoint of response, defined as hematocrit control (Hct <45%), absence of therapeutic phlebotomy, and completion of the trial regimen during part 2, in phlebotomy-dependent patients with PV[9]
- Patients in REVIVE who enrolled in the open-label extension portion of the study were eligible to continue receiving rusfertide in the ongoing open-label phase 3 THRIVE extension study (NCT06033586)

OBJECTIVE

- To present long-term results from patients who enrolled in REVIVE and THRIVE, including data on the occurrence of TEs and other clinical events relevant to patients with PV

METHODS

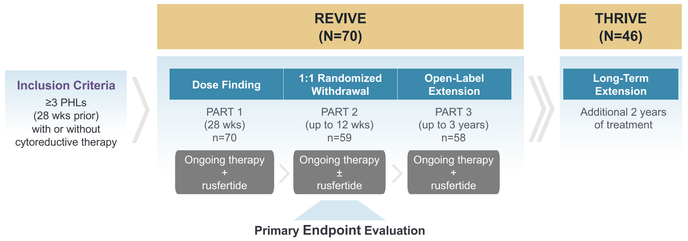
- This post hoc analysis included all patients who enrolled in REVIVE (intention-to-treat [ITT] population) and patients who transitioned to THRIVE
- TEs (arterial and venous) and hemorrhage terms were defined according to the US FDA's Office of New Drugs Custom Medical Queries version 4.0 standards
- Thrombosis-free survival (TFS) was defined as absence of death or arterial (eg, ischemic or hemorrhagic stroke, myocardial infarction [MI], transient ischemic attack [TIA]) or venous thrombosis (eg, pulmonary embolism [PE], deep vein thrombosis [DVT], abdominal/splanchnic thrombosis) events
- Event-free survival (EFS) was defined as TFS and absence of grade ≥3 hemorrhage or post-PV progression event (eg, acute myeloid leukemia [AML], myelodysplastic syndromes, myelofibrosis [MF])
- Median (95% confidence interval [CI]) time to TFS and EFS was calculated overall and in certain subgroups (eg, PV risk category, prior cytoreductive therapy [CRT])
- The data cutoff date for this analysis was 10 December 2025, with a median follow-up of 4.4 years

RESULTS

Patients

- Seventy patients enrolled in REVIVE (median age, 58 years; male, 70%; high-risk PV, 55.7%; use of concurrent CRT, 47.1%) (**Table 1**)
  - Of these 70 patients, 13 (18.6%) had a history of TEs prior to study entry
  - Forty-six of the 70 patients (65.7%) who enrolled in REVIVE transitioned to the open-label THRIVE extension study (**Figure 1**)

Figure 1. Patient Enrollment in REVIVE and THRIVE



PHL, therapeutic phlebotomy; wks, weeks.
For THRIVE, N denotes the total number of patients who transitioned from REVIVE to THRIVE.

- In THRIVE, the median (range) age of patients, calculated at the start of REVIVE for those who rolled over into THRIVE, was 58 (27-77) years; more than half had high-risk PV (**Table 1**)

Table 1. REVIVE and THRIVE Baseline Patient Demographics and Disease Characteristics

Characteristic	Phase 2 REVIVE Study (N=70)	Phase 3 THRIVE Extension Study (N=46)
Age, years, median (range)	58 (27-77)	58 (27-77)
Sex, n (%)		
Male	49 (70.0)	34 (73.9)
Female	21 (30.0)	12 (26.1)
Disease characteristics		
Risk category, n (%)		
High risk (age ≥60 years old and/or prior TE)	39 (55.7)	26 (56.5)
Low risk	31 (44.3)	20 (43.5)
Prior history of TEs, n (%)[a]		
Yes	13 (18.6)	9 (19.6)
No	57 (81.4)	37 (80.4)
Age at PV onset, years, median (range)	55.0 (5-74)	54.5 (26-74)
PV duration, years, median (range)	2.6 (0-35)	2.5 (0-22)
Concurrent CRT, n (%)		
No (PHL only)	37 (52.9)	21 (45.7)
Yes (PHL + CRT)	33 (47.1)	25 (54.3)

CRT, cytoreductive therapy; PV, polycythemia vera; PHL, therapeutic phlebotomy; SD, standard deviation; TE, thromboembolic event.
[a]Prior to initiation of dosing in the phase 2 REVIVE study.

Treatment exposure and follow-up

- In REVIVE (N=70), median (range) duration of rusfertide exposure was 2.5 (0.06-4.1) years
  - In the 46 patients who transitioned from REVIVE to THRIVE, median (range) duration of rusfertide exposure across both studies was 4.3 (2.7-5.5) years

Thromboembolic and hemorrhagic events

- After a median (95% CI) follow up of 4.4 (3.6-4.6) years, 7 of 70 patients (10.0%) had ≥1 on-study TE (**Table 2**)
  - Six of these 7 patients had onset of their event during REVIVE
- All 7 patients with on-study TE(s) had prior risk factors (eg, baseline leukocytosis) and high-risk PV
  - Four patients had TEs prior to study entry (3 venous, 2 arterial)
  - Five were receiving hydroxyurea at study entry
- Six of 7 patients with on-study TEs continued rusfertide after the event
  - Three patients remained on treatment at the data cutoff date
- The incidence rate (95% CI) of TEs in REVIVE and THRIVE was 3.0 (0.7, 5.3) per 100 patient-years

Table 2. Thromboembolic Events By Risk Group

Patient	Age/Sex	Prior History of TE	TE(s) on Study	Time Since PV Diagnosis to TE, weeks	Time Since TE Onset to Last Dose Date, weeks	Other Risk Factors	CRT at Baseline
1	72/F	None	Ischemic stroke	640.4	95.6	Hypertension, dyslipidemia	HU
2	63/M	Mesenteric arterial occlusion, acute myocardial infarction	Mesenteric arterial occlusion	839.4	78.1	Coronary artery disease, dyslipidemia, elevated WBCs[a]	HU
3	69/F	Portal vein thrombosis	Acute myocardial infarction Acute myocardial infarction	902.6	178.3	Hypertension, elevated WBCs[a]	HU
4	77/M	Deep vein thrombosis	Transient ischemic attack	470.4	172.9	Hypertension, dyslipidemia, peripheral vascular disease,elevated WBCs[a]	None
5	66/F	None	Pulmonary embolism	482.1	0.4	Smoking, elevated WBCs[a]	HU
6	60/F	None	Transient ischemic attack	257.3	39.9	Elevated WBCs[a]	None
7	72/M	Deep vein thrombosis	Stroke	443.4	16.9	Hypertension, dyslipidemia, peripheral vascular disease,elevated WBCs[a]	HU

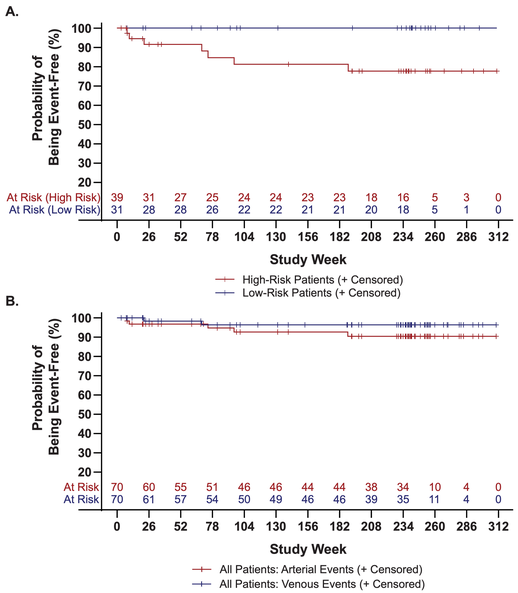
CRT, cytoreductive therapy; HU, hydroxyurea; TE, thromboembolic event; WBC, white blood cells.
TE onset occurred during REVIVE for patients 1-6 and during THRIVE for patient 7.
[a]Elevated WBCs defined as ≥11×10^9/mL.

- All TEs occurred in high-risk patients; there were no TEs in low-risk patients
- One patient with a medical history of hematomas experienced ≥1 grade 3 hemorrhage event (peritoneal and left thigh hematomas, both of which were considered unrelated or unlikely related to study treatment)
- No patients died on either study

REVIVE and THRIVE: Thrombosis-free and event-free survival (TFS and EFS)

- Median (95% CI) TFS was not reached in the ITT population
  - Median (95% CI) TFS was also not reached in patients with low- or high-risk PV (**Figure 2A**)
  - TFS by event type (arterial or venous event) is shown in **Figure 2B**; median TFS was not reached in either subgroup
- After 5 years, the estimated probability of remaining free from TEs was 88% (95% CI: 0.76, 0.94) in the ITT population

Figure 2. A) Thrombosis-Free Survival and B) Major Arterial and Venous Thrombosis-Free Survival

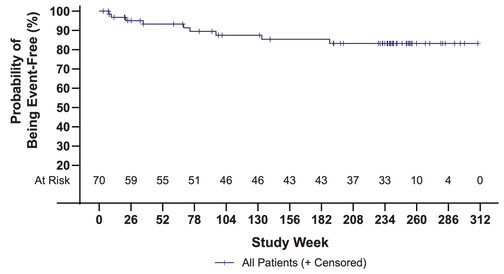


- Nine patients had ≥1 event contributing to EFS (TFS events, grade ≥3 hemorrhage, or post-PV progression), including two grade ≥3 hemorrhage events and 2 post-PV progression events (AML and MF) (**Figure 3**)
- After a median (95% CI) follow up of 4.4 (2.7-4.6) yrs, median EFS was also not reached in the ITT population or in any of the investigated subgroups

Progression and other clinically relevant events

- Two patients (2.9%) experienced post-PV progression events (1 AML, 1 MF); both had high-risk PV, with 3.5 and 5.4 years duration since PV onset, respectively. The MF patient did not receive concurrent CRT, and the AML patient received concurrent hydroxyurea.

Figure 3. Event-Free Survival



CONCLUSIONS

- After >4 years of follow-up, 10% of patients who enrolled in the phase 2 REVIVE and the phase 3 THRIVE studies had a TE
  - All of these patients had high-risk PV and other risk factors at study entry
  - In THRIVE, we have not observed any TEs in patients with low-risk PV
  - Approximately 70% of patients with prior TEs (9 of 13) remained free of TEs while on study
- The incidence of TEs in REVIVE and THRIVE was approximately 3 per 100 patient-years and is consistent with what has been reported in the literature[11]
- Two of 70 patients (2.9%) had a post-PV progression event
- Overall, these long-term data provide additional information about the occurrence of TEs and other events following rusfertide exposure that are of clinical significance in the setting of PV
- Long-term follow-up will continue to further investigate TEs, post-PV progression events, and survival following rusfertide exposure in the phase 3 setting

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