SUBGROUP ANALYSIS OF ADVERSE EVENTS FOLLOWING RUSFERTIDE DOSING IN REVIVE: A PHASE 2 STUDY IN PATIENTS WITH POLYCYTHEMIA VERA

Naveen Pemmaraju, MD[1], Srdan Verstovsek, MD, PhD[1], Marina Kremyanskaya, MD, PhD[2], Frank Valone, MD[3], Nishit B Modi, PhD[3], Sarita Khanna, PhD[3], Paula G O'Connor, MD, Suneel K Gupta, PhD[3], Ronald Hoffman, MD[2]

[1]M.D. Anderson Cancer Center, University of Texas, Houston, TX; [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Protagonist Therapeutics, Inc, Newark, CA

Introduction

Rusfertide (PTG-300) is a potent mimetic of hepcidin that binds to ferroportin causing it to be internalized and degraded, thereby decreasing iron availability to the bone marrow and reducing aberrant erythrocytosis. In the phase 2 REVIVE study (PTG-300-004; NCT04057040) of patients with polycythemia vera (PV), rusfertide treatment resulted in sustained control of hematocrit (HCT) at <45% and eliminated requirement for therapeutic phlebotomy (TP) in 84% of patients. Rusfertide was well tolerated, with no grade 4 or 5 treatment-emergent adverse events (TEAEs) [Hoffman, ASH 2021]. We present an analysis of the rusfertide TEAE profile in subgroups of interest.

Methods

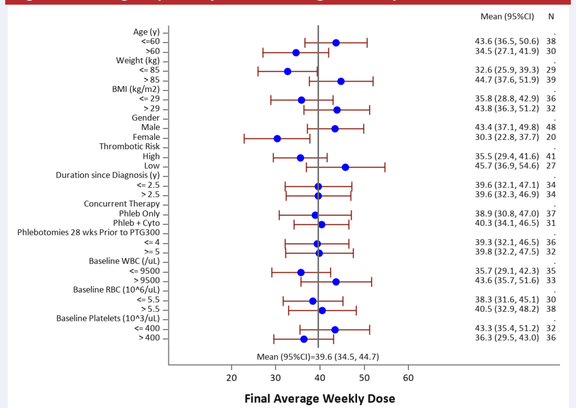
Patients with TP-dependent (i.e. ≥3 TPs within 6-month period) PV were eligible for REVIVE, which comprised 3 parts

- A 28-week open-label, dose-finding
- A 12-week double-blind randomized withdrawal
- A long-term (3 year) extension

In the dose-finding phase, subcutaneous rusfertide doses (10-120 mg) were administered with TP or with TP plus prior stable cytoreductive agents, with individualized dose titration for rusfertide to maintain HCT <45%. This analysis focuses on the 70 patients enrolled in the study with ≥8 weeks of exposure to study treatment. Incidence of treatment emergent adverse events with an incidence of ≥15% were examined in various subgroups:

- Phlebotomy alone (TP) vs Phlebotomy+Cytoreductive Therapy (CRT)
- Rusfertide dose (≤20 mg, 21 to ≤40 mg, >40 mg)
- High-Risk vs Low-Risk
- Gender (Male, Female)
- Weight (≤85 kg vs >85 kg)
- Duration since diagnosis (≤2.5 y vs >2.5 y)

Figure 1. Subgroup Analyses of Average Weekly Dose in Part 1



Error bars represent 95% confidence interval of the mean (vertical line) Data cutoff 10-20-2022

Results

- Average weekly rusfertide dose was comparable in all subgroups except those weighing ≤85 kg and female, who had average weekly doses lower than the mean (Figure 1).
- No dose relationship was noted for TEAEs, including injection site reactions (ISRs), apart for general expected dose-related pharmacologic effects (Table 1)
- The majority of TEAEs (84%) were ≤Grade 2. There were no Grade 4 or 5 TEAEs. Grade 3 TEAEs were noted in 16% of patients, with all Grade 3 TEAEs, except syncope, noted in single subjects. Syncope was noted in 2 subjects (1 male and 1 female; 3%).
- Overall incidence of TEAEs was similar across all subgroups. Some differences noted in individual TEAEs between subgroups (Table 2A-2E).
- A higher incidence of selected ISR were noted in the TP alone group (Table 2A), Low-Risk patients (Table 2B), patients weighing less than 85 kg (Table 2C), newly diagnosed patients (Table 2D), and Women (Table 2E).
- ISRs decreased with time (Figure 2).
- Rusfertide controlled HCT and decreased red blood cell counts. This was often accompanied by small (<20%) early increases in mean platelet counts
- Secondary malignancies were identified in 6 patients. Five of these 6 patients had NMSCs. All patients had either prior history of cancer or a pre-existing lesion, and all except one, had prior or concurrent CRT with hydroxyurea or ruxolitinib, each of which are known to be associated with increased risk of NMSC (Verner 2014, Lin 2022).

Table 1. Summary of Treatment Emergent Adverse Events Occurring in ≥15% Subjects and Relationship to Rusfertide Dose

	All Subjects (N=70)	≤20 mg (N=13)	21 to≤40 mg (N=36)	>40 mg (N=21)
TEAEs	69 (98.6)	12 (92.3)	36 (100)	21 (100)
Injection site reaction	61 (87.1)	11 (84.6)	30 (83.3)	20 (95.2)
Injection site erythema	45 (64.3)	10 (76.9)	24 (66.7)	11 (52.4)
Injection site pain	29 (41.4)	6 (46.2)	11 (30.6)	12 (57.1)
Injection site pruritus	26 (37.1)	4 (30.8)	15 (41.7)	7 (33.3)
Injection site mass	16 (22.9)	2 (15.4)	9 (25.0)	5 (23.8)
Injection site swelling	15 (21.4)	0	10 (27.8)	5 (23.8)
Injection site bruising	13 (18.6)	3 (23.1)	7 (19.4)	3 (14.3)
Injection site irritation	13 (18.6)	4 (30.8)	4 (11.1)	5 (23.8)
Fatigue	21 (30.0)	7 (53.8)	9 (25.0)	5 (23.8)
Pruritus	19 (27.1)	3 (23.1)	10 (27.8)	6 (28.6)
Arthralgia	16 (22.9)	1 (7.7)	9 (25.0)	6 (28.6)
Headache	16 (22.9)	3 (23.1)	7 (19.4)	6 (28.6)
Dizziness	15 (21.4)	3 (23.1)	6 (16.7)	6 (28.6)
Nausea	15 (21.4)	2 (15.4)	7 (19.4)	6 (28.6)
Anemia	13 (18.6)	2 (15.4)	6 (16.7)	5 (23.8)
COVID-19	12 (17.1)	2 (15.4)	5 (13.9)	5 (23.8)

Data cutoff for AE tables: 10/20/2022

Table 2. Summary of TEAEs with ≥10% Difference in Incidence between Subgroups

A. Treatment	TP Alone (N=37)	TP + CRT (N=33)
TEAEs	36 (97.3)	33 (100)
Injection site reaction	34 (91.9)	27 (81.8)
Injection site pruritus	17 (45.9)	9 (27.3)
Fatigue	14 (37.8)	7 (21.1)
Pruritus	8 (21.6)	11 (33.3)

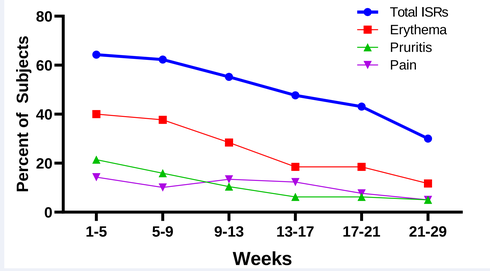
C. Weight	≤85 kg (N=30)	>85 kg (N=40)
TEAEs	29 (96.7)	40 (100)
Injection site reaction	26 (86.7)	35 (87.5)
Injection site erythema	21 (70.0)	24 (60.0)
Injection site pruritus	13 (43.3)	13 (32.5)
Injection site mass	5 (16.7)	11 (27.5)
Injection site bruising	8 (26.7)	5 (12.5)
Headache	10 (33.3)	6 (15.0)
COVID-19	7 (23.3)	5 (12.5)

E. Gender	Male (N=49)	Female (N=21)
TEAEs	48 (98.0)	21 (100)
Injection site reaction	40 (81.6)	21 (100)
Injection site erythema	29 (59.2)	16 (76.2)
Injection site pruritus	14 (28.6)	12 (57.1)
Fatigue	11 (22.4)	10 (47.6)
Pruritus	10 (20.4)	9 (42.9)
Headache	7 (14.3)	9 (42.9)
Dizziness	7 (14.3)	8 (38.1)
Nausea	8 (16.3)	7 (33.3)
Anemia	7 (14.3)	6 (28.6)

B. Risk	High (N=43)	Low (N=27)
TEAEs	43 (100)	26 (96.3)
Injection site reaction	36 (83.7)	25 (92.6)
Injection site erythema	25 (58.1)	20 (74.1)
Injection site pain	15 (34.9)	14 (51.9)
Injection site pruritus	14 (32.6)	12 (44.4)
Injection site swelling	5 (11.6)	10 (37.0)
Anemia	10 (23.3)	3 (11.1)
Dyspnea	8 (18.6)	2 (7.4)

D. Duration of PV Diagnosis	≤2.5 y (N=36)	>2.5 y (N=34)
TEAEs	35 (97.2)	34 (100.0)
Injection site reaction	30 (83.3)	31 (91.2)
Injection site erythema	21 (58.3)	24 (70.6)
Injection site swelling	10 (27.8)	5 (14.7)
Injection site irritation	11 (30.6)	2 (5.9)
Fatigue	9 (25.0)	12 (35.3)
Pruritus	12 (33.3)	7 (20.6)
Headache	5 (13.9)	11 (32.4)
Nausea	5 (13.9)	10 (29.4)
Anemia	3 (8.3)	10 (29.4)

Figure 2. Incidence of Injection Site Reactions with Time



Summary

- Majority of TEAEs (84%) were ≤Grade 2. There were no Grade 4 or 5 TEAEs. 16% patients experienced Grade 3 TEAEs.
- No meaningful dose relationship was noted for any of the common TEAEs, including Injection Site Reactions (ISRs)
- Most TEAEs were comparable in patients receiving rusfertide with TP alone and those receiving rusfertide with TP+CRT.
- Frequency of injection site reactions decreased with time.
- Average weekly rusfertide dose was generally comparable in all subgroups except those weighing ≤85 kg/female gender
- Secondary malignancies were identified in 6 patients. Five of these 6 patients had NMSCs. All patients had either prior history of cancer or a pre-existing lesion, and all except one, had prior or concurrent CRT with hydroxyurea or ruxolitinib, each of which are known to be associated with increased risk of NMSC (Verner 2014, Lin 2022).

References

1. Hoffman R, Kremyanskaya M, Ginzburg Y, et al. Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients. Abstract #388. Presented at the 2021 American Society of Hematology Annual Meeting, December 12, 2021.
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3. Lin JQ, Li SQ, Li S, Kiamanesh EF, Aasi SZ, Kwong BY, Chang ALS. A 10-year retrospective cohort study of ruxolitinib and association with nonmelanoma skin cancer in patients with polycythemia vera and myelofibrosis. J Am Acad Dermatol 2022; 86:339-344.