Protagonist Therapeutics

Post-ASCO Update: Phase 3 VERIFY Study Results

Protagonist Therapeutics, Inc.
Newark, CA

June 2, 2025

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Phase 3 VERIFY Study: Primary Results

Data Presented at 2025 American Society of Clinical Oncology (ASCO) Annual Meeting (Plenary Presentation)

by Andrew T. Kuykendall, MD (Moffitt Cancer Center, Tampa, FL)

Sunday June 1, 2025

Arturo Molina, MD, MS, FACP
Chief Medical Officer
Protagonist Therapeutics, Inc.

Key Takeaway Points from Phase 3 VERIFY Study in Polycythemia Vera (PV)

VERIFY is a **global, randomized, double-blind phase 3 study** investigating rusfertide or placebo with current standard-of-care therapy in patients with PV

VERIFY met its prespecified primary endpoint (response) **and all four key secondary endpoints**, including reduction in phlebotomy and improvement in symptoms (assessed by PRO measures) vs. placebo

Rusfertide was well tolerated and had a safety profile that was consistent with prior observations in phase 2 studies of patients with PV, including REVIVE

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Rusfertide Phase 3 **VERIFY** Study

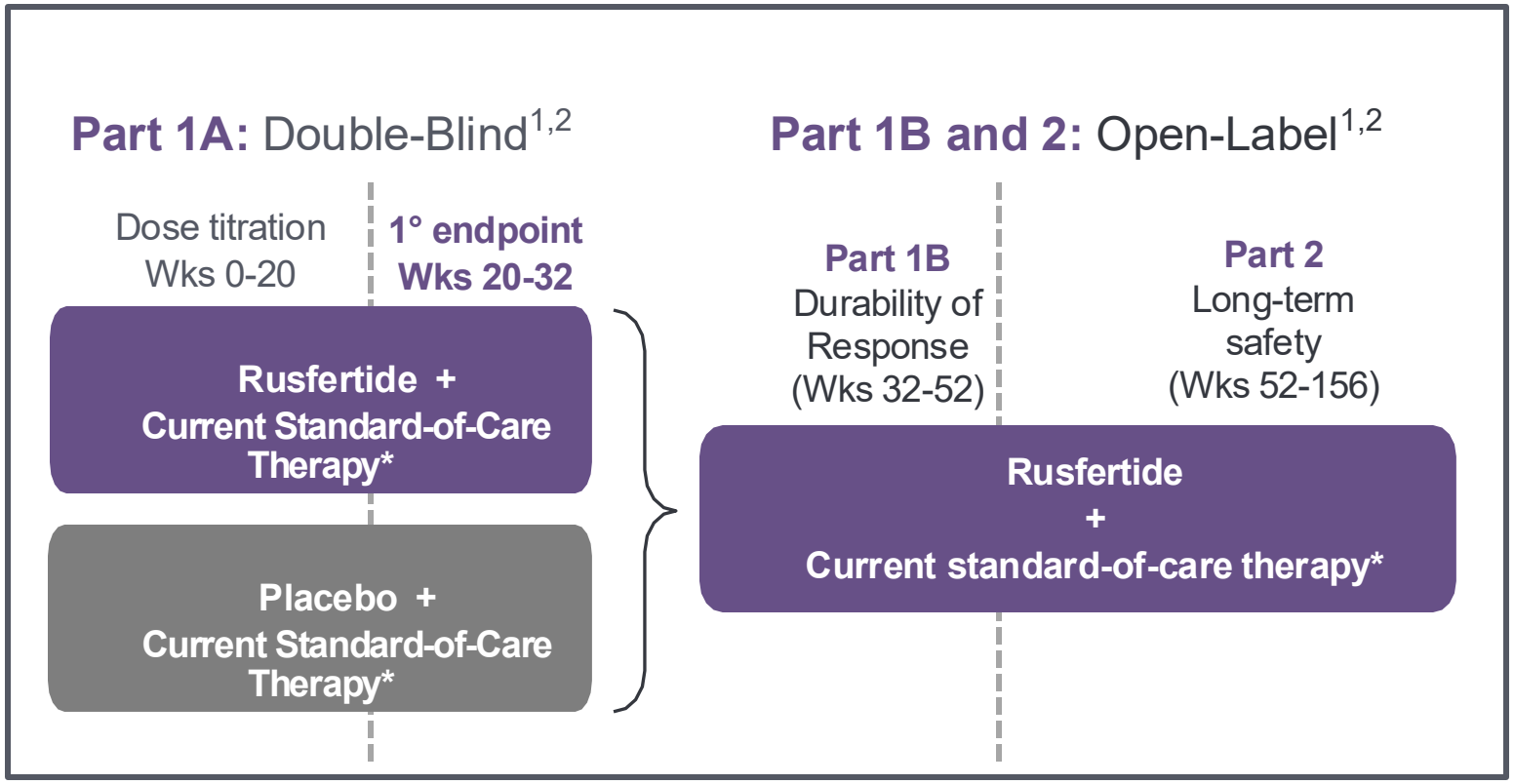
Clinical Study Design and Topline Results

Inclusion Criteria

≥3 PHL (28 wks prior)
OR
≥5 PHL (1 year prior)

N = 293

1:1 randomization



Primary endpoint:[3]

Wks 20-32

1. **Clinical Response: rusfertide vs placebo**

Key 2° endpoints:

Wks 0-32

1. **Average number of PHLs[4]**
2. **Proportion of patients with Hct <45%**
3. **Average PROMIS Fatigue SF-8a Score[5-6]**
4. **Average MFSAF Total Symptom Score[7-8]**

*Therapy could include therapeutic phlebotomy and/or cytoreductive therapy.

1. ClinicalTrials.gov. NCT05210790. https://clinicaltrials.gov/ct2/show/NCT05210790;
2. ASCO'24: Bankar A, et al. VERIFY: A randomized controlled phase 3 study of the hepcidin mimetic rusfertide (PTG-300) in patients with polycythemia vera (PV). J Clin Oncol;2024;42;16_suppl. TPS6592.
3. US primary endpoint; 4. EU primary endpoint
5. Garcia SF, et al. *J Clin Oncol*. 2007;25:5106-12; 6. Cella D, et al. *J Clin Epidemiol*. 2016;73:128-34
7. Mesa RA, et al. *Leuk Res*. 2009;33:1199-203; 8. Gwaltney C, et al. *Leuk Res*. 2017;59:26-31

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Baseline Demographics and Disease Characteristics Well Balanced Across Groups

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)	Total (N=293)
Age, years, median (range)	57 (27-82)	58 (28-86)	57 (27-86)
Gender, n (%)			
Male	108 (74.0)	106 (72.1)	214 (73.0)
Female	38 (26.0)	41 (27.9)	79 (27.0)
Risk Category, n (%)			
High risk (age ≥60 years old and/or prior TE)	70 (47.9)	66 (44.9)	136 (46.4)
Disease Characteristics			
Age at PV diagnosis (years), median (range)	51 (22-81)	53 (17-84)	52 (17-84)
PV duration (years), median (range)	3 (0.2-29.2)	2.8 (0.2-26.4)	2.9 (0.2-29.2)
Phlebotomy History – 28 Weeks Prior to Study Treatment			
Number of TPs, mean ± SD	4.1 ± 1.4	4.2 ± 1.6	4.2 ± 1.5
Patients requiring ≥7 TPs, n (%)	7 (4.8)	16 (10.9)	23 (7.8)

CSC, current standard-of-care; PV, polycythemia vera; SD, standard deviation; TE, thromboembolic event; TP, therapeutic phlebotomy. Data cutoff: 7 January 2025

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Concurrent Cytoreductive Therapy During Part 1a

n (%)	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)	Total (N=293)
Patients With Concurrent Cytoreductive Medication	81 (55.5)	83 (56.5)	164 (56.0)
Hydroxyurea	57 (39.0)	58 (39.5)	115 (39.2)
Interferons			
Interferon, peginterferon alpha-2a, or ropeginterferon alfa-2b	20 (13.7)	19 (12.9)	39 (13.3)
JAK1/JAK2 Inhibitors			
Ruxolitinib	3 (2.1)	5 (3.4)	8 (2.7)

CSC, current standard-of-care; JAK, Janus Kinase.

Data cutoff: 7 January 2025

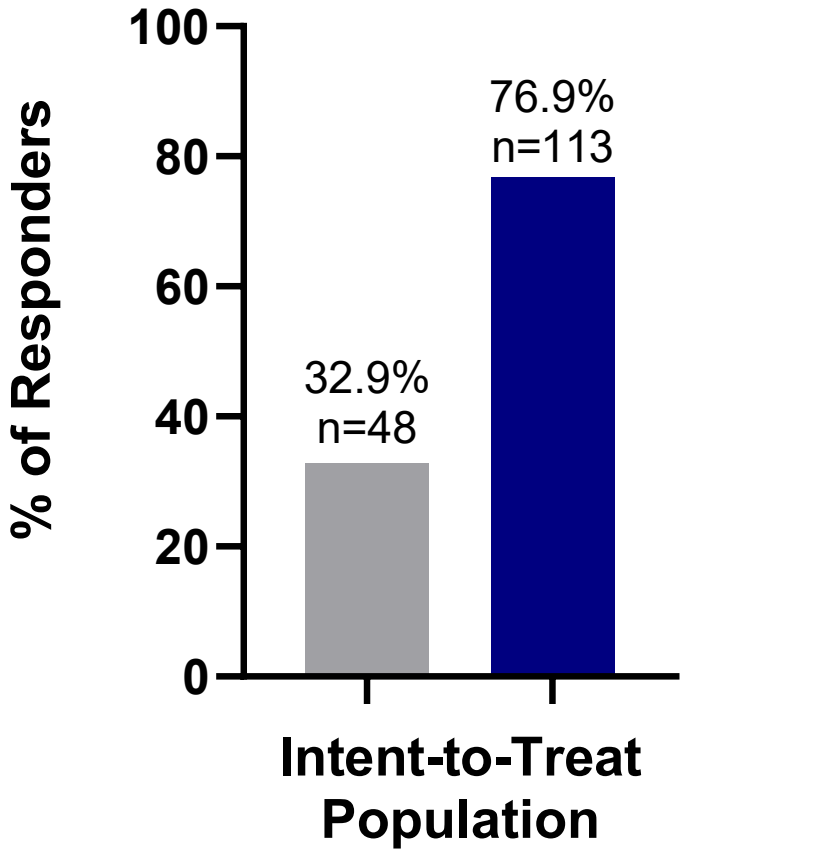
- Demographics in line with entire PV population showing generalizability of the data

VERIFY Study Met Its Primary Endpoint During Weeks 20-32 (Part 1a)

US FDA Primary Endpoint

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Responders, n (%)[a]	48 (32.9)	113 (76.9)
p-value*		**<0.0001**
Non-responders, n (%)	98 (67.1)	34 (23.1)

[a]Responder = absence of phlebotomy eligibility (confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%), no phlebotomies, and completion of Part 1a.
*p-value based on Cochran-Mantel-Haenszel test.
Hct, hematocrit.



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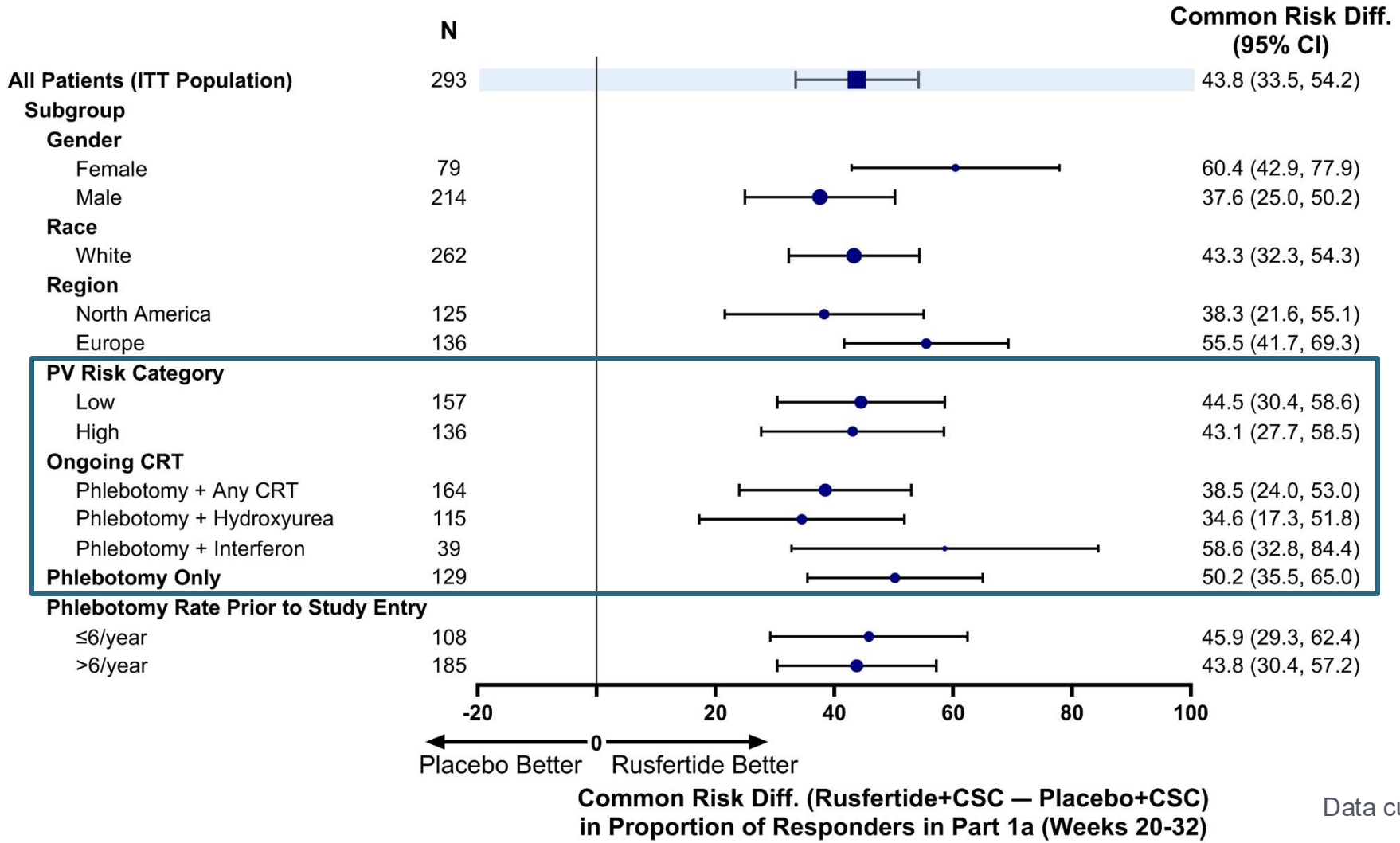
Rusfertide Benefit Maintained vs. Placebo for Response* Across Subgroups, Including Risk Status and Concurrent Therapy



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*Common risk difference for primary endpoint of response.
CRT, cytoreductive therapy; CSC, current standard-of-care; ITT, intent to treat.

Mean Number of Phlebotomies (Primary EU Endpoint) and Supportive Data (Freedom From Phlebotomy)

Key Secondary Endpoint #1: Weeks 0-32

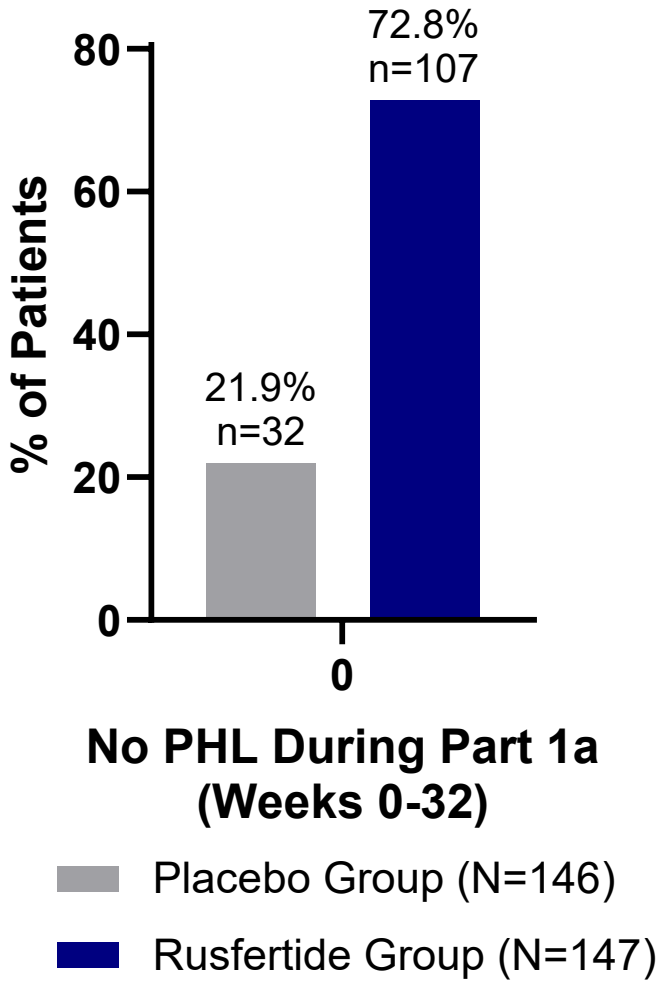
Mean Number of Phlebotomies (EU Primary Endpoint)

Number of Phlebotomies	Placebo (n=146)	Rusfertide (n=147)
Mean (SD)	1.8 (1.5)	0.5 (1.2)
p-value*	<0.0001	

*p-value associated with the LS means difference.
LS, least-squares; SD, standard deviation.

Data cutoff: 7 January 2025

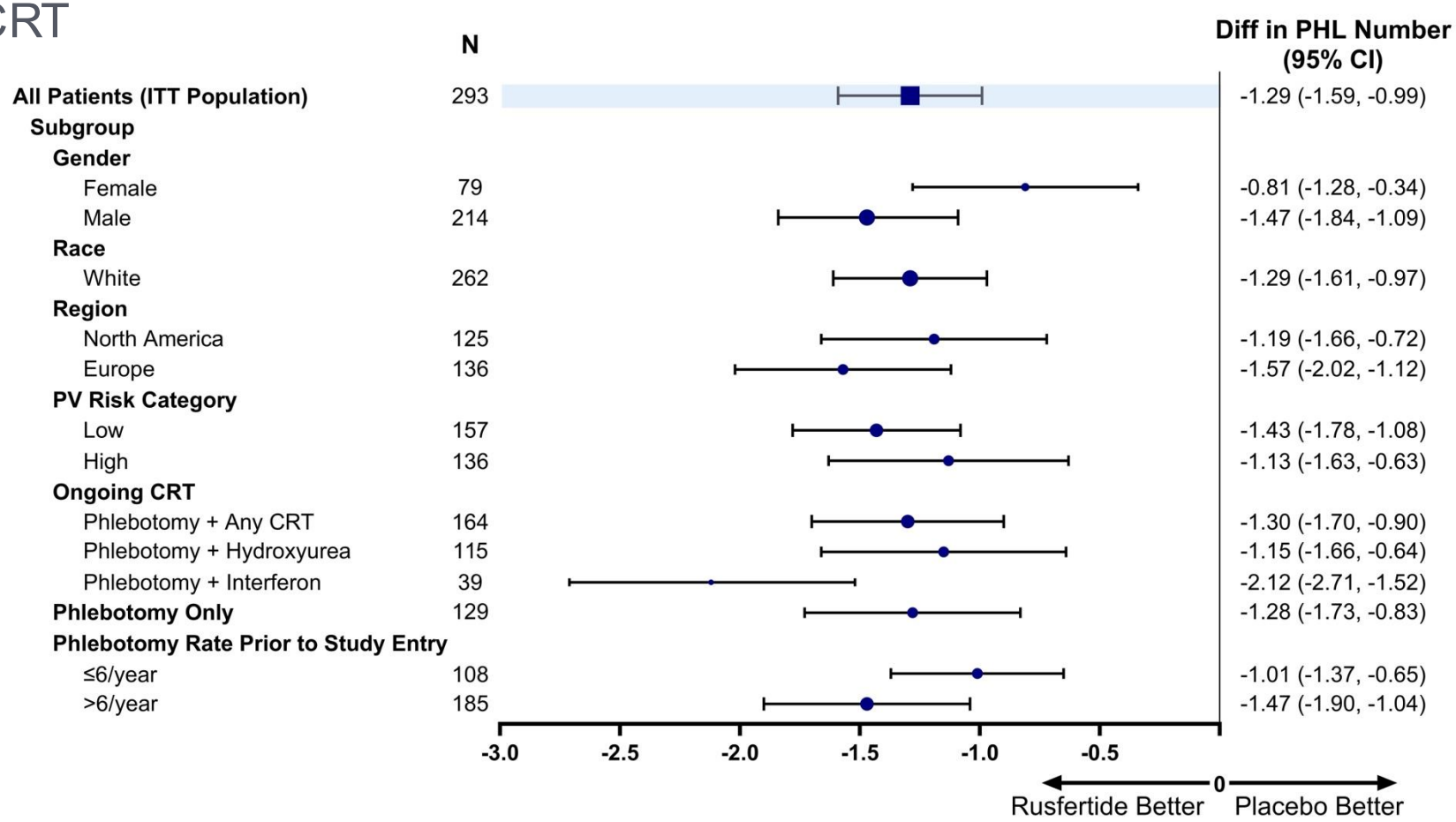
Freedom From Phlebotomy During Weeks 0-32



PHL, phlebotomy.

Rusfertide Reduced the Mean Number of PHL From Weeks 0-32 vs Placebo (p<0.0001)

- Rusfertide reduced the mean number of PHL (Weeks 0-32) vs. placebo by a statistically significant margin across subgroups, including PV risk category, geographic region, and use of concurrent CRT



Diff in PHL Number = (Rusfertide+CSC — Placebo+CSC LS Means Difference) in Part 1a (Weeks 0-32)

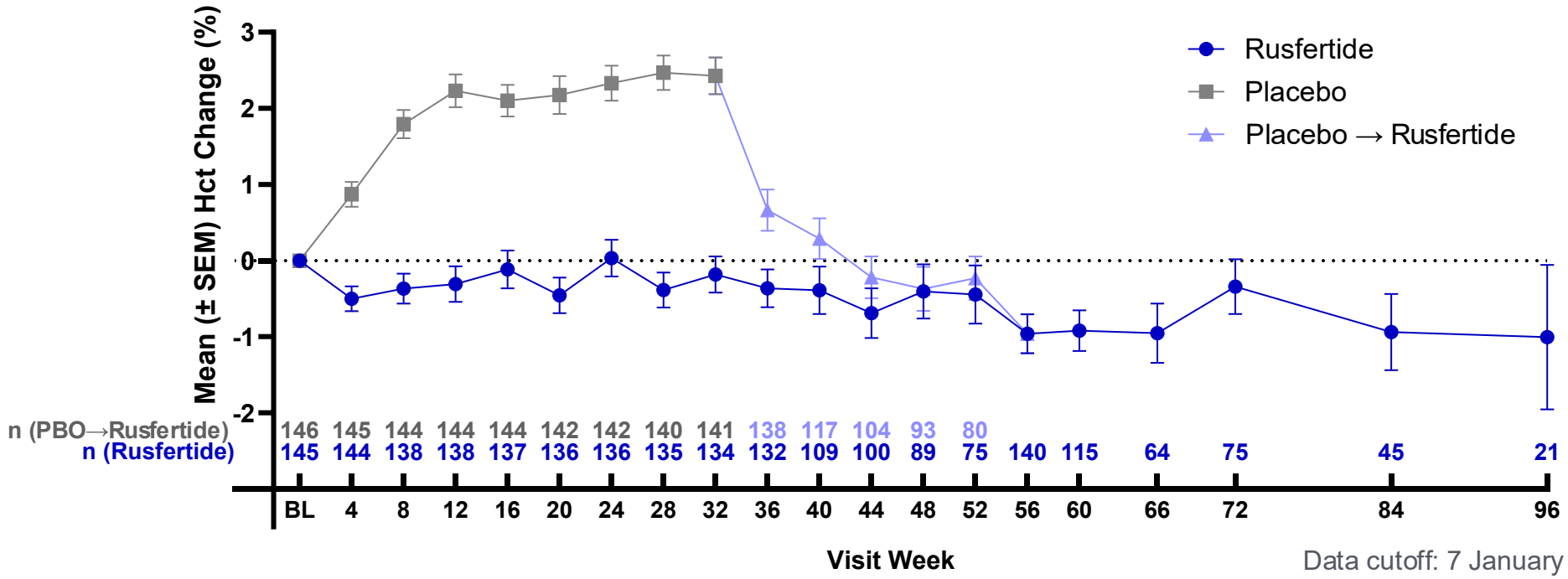
Data cutoff: 7 January 2025

Rusfertide + CSC More Likely to Maintain Hct <45% From Weeks 0-32 vs Placebo + CSC

Key Secondary Endpoint #2

	Placebo (n=146)	Rusfertide (n=147)
Hct <45% (Baseline through Week 32), n (%)[a]	21 (14.4)	92 (62.6)
p-value*		**<0.0001**

[a]Hct <45% from baseline through Week 32 (a single Hct ≥45% was allowed, excluding intercurrent events classified as non-responders).
*Cochran-Mantel-Haenszel test.
Hct, hematocrit.



Data cutoff: 7 January 2025

Hct, hematocrit; PBO, placebo; SEM, standard error of measurement; SOC, standard-of-care.

VERIFY: Key PRO-Related Secondary Endpoints at Week 32

Includes All Patients* Regardless of Symptom Status at Baseline

			Endpoint Description
Instrument	**Symptom(s)**		**Comparison of rusfertide to placebo:**
PROMIS Fatigue SF-8a[1,2]	SF-8a	Fatigue	• Mean change from baseline at end of Part 1a (Week 32) in the PROMIS SF-8a total T-score
MFSAF version 4.0[3,4]	TSS-7	Fatigue	• Mean change from baseline at end of Part 1a (Week 32) in the MFSAF v4.0 TSS7
		Night sweats	
		Itching	
		Abdominal discomfort	
		Pain under the ribs	
		Early satiety	
		Bone pain	

*Patients were not required to have symptoms (e.g., fatigue, night sweats, itching, etc.) to enroll in VERIFY.

MFSAF TSS7, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score 7; PRO, patient reported outcomes; PROMIS Fatigue SF-8a, Patient Reported Outcomes Measurement Information System (PROMIS®) Fatigue Short Form 8a; PV, polycythemia vera; TSS, total symptom score.

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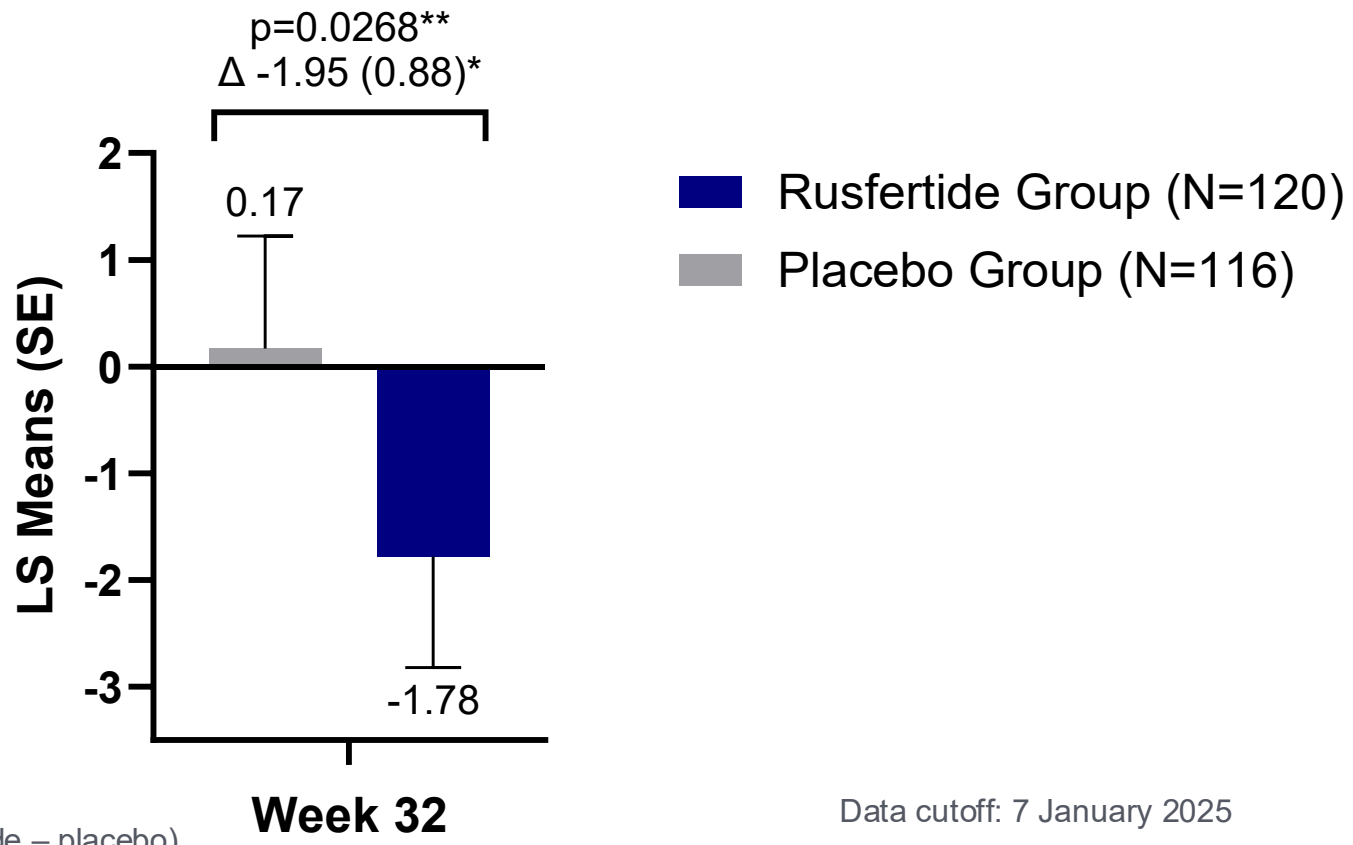
1. Garcia SF, et al. *J Clin Oncol*. 2007;25:5106-12; 2. Cella D, et al. *J Clin Epidemiol*. 2016;73:128-34; 3. Mesa RA, et al. *Leuk Res*. 2009;33:1199-203; 4. Gwaltney C, et al. *Leuk Res*. 2017;59:26-31.

Rusfertide Demonstrated an Improvement in the PROMIS Fatigue SF-8 vs Placebo at Week 32

Key Secondary Endpoint #3

LS Means Difference at Week 32:



Data cutoff: 7 January 2025

*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error; SF, short form.

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PROMIS Fatigue SF-8a Total T-Score (Week 32)

Key Secondary Endpoint #3: Additional Context

- The PROMIS Fatigue Short Form 8a contains 8 questions that ask about fatigue
  - Individual scores between 1 (not at all) and 5 (very much) used to generate a raw score, which is then converted to a T-score
- There was a statistically significant improvement* in the PROMIS Fatigue SF-8a with rusfertide vs placebo at Week 32 during the end of Part 1a
  - LS means use modeling and include covariates and baseline adjustments
- We look forward to presenting additional data at future medical meetings, including additional exploratory analyses

*LS mean (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error; SF, short form.

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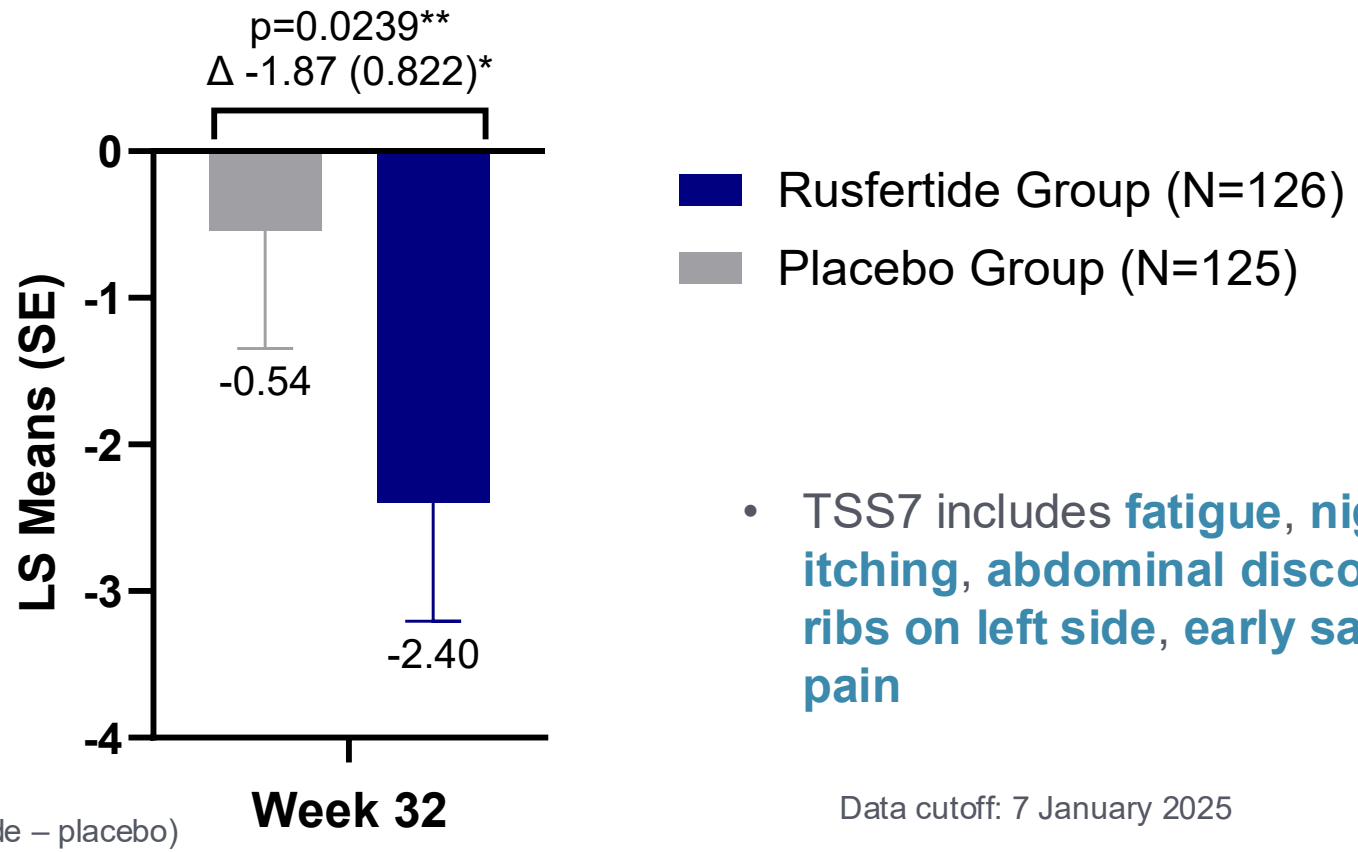
Rusfertide Demonstrated an Improvement in the MFSAF TSS7 vs Placebo at Week 32

Key Secondary Endpoint #4

LS Means Difference at Week 32:



- TSS7 includes **fatigue**, **night sweats**, **itching**, **abdominal discomfort**, **pain under ribs on left side**, **early satiety**, and **bone pain**

Data cutoff: 7 January 2025

*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; MFSAF TSS7, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score-7 item; SE, standard error.

Improvement With Rusfertide in MFSAF TSS7 at Week 32

Key Secondary Endpoint #4: Additional Context

- MFSAF scored between 0 (absent) and 10 (worst imaginable) for each individual symptom
  - Total symptom score (TSS) out of 70
- Unlike the PROMIS Fatigue SF-8a, raw data are used to score the TSS in the MFSAF
- There was a statistically significant improvement* in the MFSAF TSS7 in the rusfertide vs placebo groups at Week 32 (end of Part 1a)
  - LS means use modeling and include covariates and baseline adjustments
- To our knowledge, no other randomized Phase 3 trials in PV have demonstrated a statistically significant improvement with the MFSAF
  - Results from VERIFY confirm data from the open-label phase 2 results from REVIVE (MPN-SAF)
- Like the PROMIS Fatigue SF-8a data, we look forward to presenting additional data from the MFSAF and other PRO-focused endpoints at future meetings

*LS mean (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; MFSAF TSS7, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score-7 item; SE, standard error.

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Exposure and Treatment-Emergent Adverse Events (Part 1a)

- Median treatment exposure was 32 weeks in both groups
  - Median (min, max) dose was 30 (10, 90) mg in the rusfertide group
- The most common TEAEs in the rusfertide group included localized injection site reactions and anemia
- Discontinuation rates due to TEAEs were 2.7% (placebo) and 5.5% (rusfertide)

Most Frequent TEAEs (≥6.5% in either group) in Part 1a, n (%)	Placebo (n=146)	Rusfertide (n=145)
Patients with at least 1 TEAE	126 (86.3)	129 (89)
Injection site reactions[a]	48 (32.9)	81 (55.9)
Anemia	6 (4.1)	23 (15.9)
Fatigue	23 (15.8)	22 (15.2)
Headache	17 (11.6)	15 (10.3)
COVID-19	16 (11.0)	14 (9.7)
Pruritus	14 (9.6)	14 (9.7)
Diarrhea	8 (5.5)	12 (8.3)
Dizziness	9 (6.2)	12 (8.3)
Arthralgia	12 (8.2)	11 (7.6)
Constipation	11 (7.5)	11 (7.6)
Abdominal distension	8 (5.5)	10 (6.9)
Thrombocytosis	0	10 (6.9)

Data cutoff: 7 January 2025

*Safety analysis set.
AE, adverse event; TEAE, treatment-emergent adverse event.

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Cancer Events and Serious TEAEs (Part 1a)*

- 10 skin malignancies (including 1 melanoma) detected prior to randomization
- During Part 1a, non-PV cancer events were reported in 8 patients

Cancer Events	Placebo (n=146)	Rusfertide (n=145)
Patients with ≥1 Cancer Event, n (%)	**7 (4.8)**	**1 (0.7)**
Basal cell carcinoma	3 (2.1)	0
Squamous cell carcinoma	1 (0.7)	1 (0.7)
Malignant melanoma	1 (0.7)	0
Colorectal cancer	1 (0.7)	0
Prostate cancer	1 (0.7)	0

- Serious AEs occurred in 3.4% (rusfertide) and 4.8% (placebo) of patients (none related to rusfertide)
- There was 1 TE (acute MI; occurred ~2 weeks after treatment initiation) reported in the rusfertide group

*Safety analysis set. Data cutoff: 7 January 2025

AE, adverse event; MI, myocardial infarction; TE, thromboembolic event; TEAE, treatment-emergent adverse event.

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Phase 3 VERIFY Conclusions

- In the Phase 3 VERIFY study that included patients with PV receiving SOC therapy, rusfertide met its primary endpoint and all four key secondary endpoints vs. placebo
  - Rusfertide:
    - Significantly reduced the mean number of PHL and improved Hct control in the desired target range (Hct <45%) vs. placebo
    - Demonstrated a statistically significant improvement in symptoms measured by two PRO instruments vs. placebo
- Rusfertide was well tolerated and had a safety profile consistent with prior studies
- **Rusfertide represents a potential new treatment option for PV**
  - These data will be used to file marketing authorizations throughout the world

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CRT, cytoreductive therapy; Hct, hematocrit; PHL, phlebotomy; PRO, patient-reported outcome; PV, polycythemia vera.

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Closing Remarks

Dinesh V. Patel, PhD
Director, President, and CEO
Protagonist Therapeutics, Inc.
Newark, CA

Rusfertide has the Potential to be a New SOC in PV Based on Ph3 Data

Peak Revenue Potential of $1-2 Billion[1]

Treatment Goals	Emerging Rusfertide Profile[2]
Consistently maintaining Hct<45% • Uncontrolled Hct is associated with ~4x higher risk of death from cardiovascular causes or thrombotic events[3] • Up to 78% of patients have uncontrolled Hct>45%[4]	✓ **63%** of patients maintained HCT<45% vs 14% placebo
• Deliver efficacy independent of current standard of care treatment	✓ Demonstrated efficacy against placebo + background SOC including, PHL, HU, JAK and interferon
Reduce burden of phlebotomies • PHLs results in iron deficiency and amplifies PV symptoms	✓ **77%** of patients didn't need a PHL in wks 20-32 ✓ **>3x LESS** mean number of PHL wks 0-32 vs placebo
Reduce treatment/symptom burden • 84% of patients report fatigue, and 23% report spending full days in bed because of symptoms	✓ Both PRO endpoints met with statistical significance
• Provide safe and effective treatment option	✓ Generally well tolerated safety profile with a majority of TEAEs being mild or moderate

1. Takeda R&D Day, December 2024
2. Target profile based on Ph3 data
3. Marchioli R, et al. *N Engl J Med*. 2013;368(1):22-33.
4. Verstovsek S, et al. *Ann Hematol*. 2023;102(3):571-581.

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Takeda Partnership

- Takeda is the perfect partner for Protagonist to help commercialize rusfertide
  - Leading hematology/oncology business worldwide
  - New strong leadership team
  - Leading Rusfertide NDA submission
    - Pre-commercialization activities underway
    - Priority near term launch for overall business

- We look forward to partnering with Takeda as they complete and submit regulatory filings for rusfertide in key markets around the world, including the United States, Europe, and Japan

Scenario	Total $$ upfront + milestones	Upfront	Payable Opt-Out	Potential Milestones	Royalty Rates	Comment
OPT-IN	$630M	$300M ✓	-	$330M	10-17% Ex-US	50:50 US profit/loss share
OPT-OUT	$1,675M	$300M ✓	$400M	$975M	14-29% worldwide	Exclusive US rights to Takeda

Rusfertide Clinical Development Program in PV

NDA Filing in Q4 2025

HEMATOLOGY

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RUSFERTIDE
Hepcidin Mimetic

Discovery/Pre-Clinical	Phase 1	Phase 2	Phase 3	Key Milestones
Polycythemia Vera (PV)				
VERIFY Ph 3, n=293				• Topline 32-Wk Primary EP results ✓
REVIVE Ph 2, n=70			✓	• Completed
THRIVE LTE, n=46			✓	• Ongoing; for REVIVE patients in OLE
PACIFIC Ph 2, Elevated Hct (>48%), n=20			✓	• Completed

Q1 2025	Q2 2025	Q3 2025	Q4 2025
❖ PV Day[1] ✓			
❖ Ph3 VERIFY topline ✓	❖ ASCO 2025 ✓		❖ NDA filing
❖ Rat 2-year carcinogenicity study ✓			

Rusfertide has **Orphan Drug** designation and **Fast Track** status for PV

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Major Upcoming Catalysts in 2025

Expected Clinical Trial Initiations, Data Readouts and Development Candidate Nominations

	2024	Q1 2025	Q2 2025	Q4 2025
Rusfertide (Takeda)	❖ *New Engl J Med,* 2024; 390:723-35, REVIVE Ph2 ❖ Ph3 VERIFY enrollment completion	❖ PV day ✓ ❖ **Topline results** ✓	❖ **ASCO plenary session** ✓	❖ **NDA filing** ❖ ASH 2025
Icotrokinra (Johnson&Johnson Innovative Medicine)	❖ *New Engl J Med,* 2024; 390:510-21, FRONTIER 1 Ph2 results ❖ Ph3 PsO **LEAD** ✓ ❖ Ph3 PsO **TOTAL** ✓	❖ Medical Conferences ❖ **Ph2b UC ANTHEM** ✓ ❖ Ph3 ICONIC-PsA 1 Initiation ✓ ❖ Ph3 ICONIC-PsA 2 Initiation ✓ ❖ Ph3 PsO ADVANCE 1 ✓ ❖ Ph3 PsO ADVANCE 2 ✓ ❖ Ph3 PP/EP study		❖ **Psoriasis NDA filing** ❖ Ph3 ICONIC-ASCEND H2H vs. Stelara ✓ ❖ New UC study ❖ New Crohn's study
Discovery	**1. PN-881** ✓ Oral IL-17 Antagonist Development Candidate (DC)		**2. Oral Obesity** DC	❖ Ph1 initiation **3. Oral Hepcidin** DC

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Thank you

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Q&A

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Arturo Molina, MD, MS, FACP
EVP and Chief Medical Officer

Samuel Saks, MD
Clinical Advisor