# Rusfertide

## Investor Call on Phase 3 PV Data Presented at ASCO 2025

June 1st, 2025 ET / June 2nd, 2025 JST

Better Health, Brighter Future

# Important Notice

For the purposes of this notice, "presentation" means this document, any oral presentation, any question and answer session and any written or oral material discussed or distributed by Takeda Pharmaceutical Company Limited ("**Takeda**") regarding this presentation. This presentation (including any oral briefing and any question-and-answer in connection with it) is not intended to, and does not constitute, represent or form part of any offer, invitation or solicitation of any offer to purchase, otherwise acquire, subscribe for, exchange, sell or otherwise dispose of, any securities or the solicitation of any vote or approval in any jurisdiction. No shares or other securities are being offered to the public by means of this presentation. No offering of securities shall be made in the United States except pursuant to registration under the U.S. Securities Act of 1933, as amended, or an exemption therefrom. This presentation is being given (together with any further information which may be provided to the recipient) on the condition that it is for use by the recipient for information purposes only (and not for the evaluation of any investment, acquisition, disposal or any other transaction). Any failure to comply with these restrictions may constitute a violation of applicable securities laws.

The companies in which Takeda directly and indirectly owns investments are separate entities. In this presentation, "Takeda" is sometimes used for convenience where references are made to Takeda and its subsidiaries in general. Likewise, the words "we", "us" and "our" are also used to refer to subsidiaries in general or to those who work for them. These expressions are also used where no useful purpose is served by identifying the particular company or companies.

The product names appearing in this document are trademarks or registered trademarks owned by Takeda, or their respective owners.

**Forward-Looking Statements**

This presentation and any materials distributed in connection with this presentation may contain forward-looking statements, beliefs or opinions regarding Takeda's future business, future position and results of operations, including estimates, forecasts, targets and plans for Takeda. Without limitation, forward-looking statements often include words such as "targets", "plans", "believes", "hopes", "continues", "expects", "aims", "intends", "ensures", "will", "may", "should", "would", "could", "anticipates", "estimates", "projects", "forecasts", "outlook" or similar expressions or the negative thereof. These forward-looking statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those expressed or implied by the forward-looking statements: the economic circumstances surrounding Takeda's global business, including general economic conditions in Japan and the United States and with respect to international trade relations; competitive pressures and developments; changes to applicable laws and regulations, including tax, tariff and other trade-related rules; challenges inherent in new product development, including uncertainty of clinical success and decisions of regulatory authorities and the timing thereof; uncertainty of commercial success for new and existing products; manufacturing difficulties or delays; fluctuations in interest and currency exchange rates; claims or concerns regarding the safety or efficacy of marketed products or product candidates; the impact of health crises, like the novel coronavirus pandemic; the success of our environmental sustainability efforts, in enabling us to reduce our greenhouse gas emissions or meet our other environmental goals; the extent to which our efforts to increase efficiency, productivity or cost-savings, such as the integration of digital technologies, including artificial intelligence, in our business or other initiatives to restructure our operations will lead to the expected benefits; and other factors identified in Takeda's most recent Annual Report on Form 20-F and Takeda's other reports filed with the U.S. Securities and Exchange Commission, available on Takeda's website at: https://www.takeda.com/investors/sec-filings-and-security-reports/ or at www.sec.gov. Takeda does not undertake to update any of the forward-looking statements contained in this presentation or any other forward-looking statements it may make, except as required by law or stock exchange rule. Past performance is not an indicator of future results and the results or statements of Takeda in this presentation may not be indicative of, and are not an estimate, forecast, guarantee or projection of Takeda's future results.

**Financial Information and Certain Non-IFRS Financial Measures**

Takeda's financial statements are prepared in accordance with International Financial Reporting Standards ("IFRS").

This presentation and materials distributed in connection with this presentation include certain financial measures not presented in accordance with IFRS, such as Core Revenue, Core Operating Profit, Core Net Profit, Core EPS, Constant Exchange Rate ("CER") change, Net Debt, EBITDA, Adjusted EBITDA, Free Cash Flow and Adjusted Free Cash Flow. Takeda's management evaluates results and makes operating and investment decisions using both IFRS and non-IFRS measures included in this presentation. These non-IFRS measures exclude certain income, cost and cash flow items which are included in, or are calculated differently from, the most closely comparable measures presented in accordance with IFRS. Takeda's non-IFRS measures are not prepared in accordance with IFRS and such non-IFRS measures should be considered a supplement to, and not a substitute for, measures prepared in accordance with IFRS (which we sometimes refer to as "reported" measures). Investors are encouraged to review the definitions and reconciliations of non-IFRS financial measures to their most directly comparable IFRS measures, which are in the financial appendix appearing at the end of this presentation.

Beginning in the first quarter of FY24, Takeda (i) changed its methodology for CER adjustments to results of subsidiaries in hyperinflation countries to present those results in a manner consistent with IAS 29, Financial Reporting in Hyperinflation Economies, and (ii) re-named Free Cash Flow as previously calculated as "Adjusted Free Cash Flow" (with "Free Cash Flow" now reported as Operating Cash Flow less Property, Plant and Equipment), and (iii) re-named Net Debt as previously calculated as "Adjusted Net Debt" (with "Net Debt" to be reported as the book value of bonds and loans less cash and cash equivalents). For more information about the changes, including how the new methodology would have impacted Takeda's FY23 results, as well as other important information about Takeda's non-IFRS measures, including the limitations on the usefulness thereof, refer to the Financial Appendix.

**Peak Revenue Potential and PTRS Estimates**

References in this presentation to peak revenue ranges are estimates that have not been adjusted for probability of technical and regulatory success (PTRS) and should not be considered a forecast or target. These peak revenue ranges represent Takeda's assessments of various possible future commercial scenarios that may or may not occur. References in this presentation to PTRS are to internal estimates of Takeda regarding the likelihood of obtaining regulatory approval for a particular product in a particular indication. These estimates reflect the subjective judgment of responsible Takeda personnel and have been approved by Takeda's Portfolio Review Committee for use in internal planning.

**Exchange Rates**

In this presentation, certain amounts presented in Japanese yen have been translated to US dollars solely for the convenience of the reader. Except where otherwise noted, these convenience translations have been made at an exchange rate of 1USD = 149.90, the Noon Buying Rate certified by the Federal Reserve Bank of New York on March 31, 2025. The rate and methodologies used for these convenience translations differ from the currency exchange rates and translation methodologies under IFRS used for the preparation of Takeda's consolidated financial statements. These translations should not be construed as a representation that the relevant Japanese yen amounts could be converted into U.S. dollars at this or any other rate.

**Medical information**

This presentation contains information about products that may not be available in all countries, or may be available under different trademarks, for different indications, in different dosages, or in different strengths. Nothing contained herein should be considered a solicitation, promotion or advertisement for any prescription drugs including the ones under development.

# Agenda

## Today's Topics

**Efficacy and Safety Results from the Ph3 Trial of Rusfertide in PV Patients**

**P.K. Morrow**
*Head of Oncology Therapeutic Area Unit*

**Market Opportunity**

**Teresa Bitetti**
*President, Global Oncology Business Unit*

**Q&A Session**

**Panelists**

**P.K. Morrow**
*Head of Oncology Therapeutic Area Unit*

**Teresa Bitetti**
*President, Global Oncology Business Unit*

# Key Takeaway Points/Conclusions



1

Phase 3 VERIFY study compared the hepcidin mimetic rusfertide to placebo (each added to current standard-of-care) in patients with polycythemia vera

2

Rusfertide met its primary endpoint, all key secondary endpoints, and had a manageable safety profile consistent with prior studies

3

Rusfertide led to statistically significant improvements in several patient reported outcome measures



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm driven by acquired *JAK2* mutations[1-3]
- PV is characterized by excessive production of blood cells which contributes to an increased risk of cardiovascular and thrombotic events
- Primary goal of PV treatment aims to reduce thrombotic risk by achieving and maintaining Hct <45%[2,3]
- Current standard-of-care for PV: phlebotomy ± cytoreductive therapy
- Frequent phlebotomy is burdensome and often insufficient for durable Hct control <45%[4-6]

Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

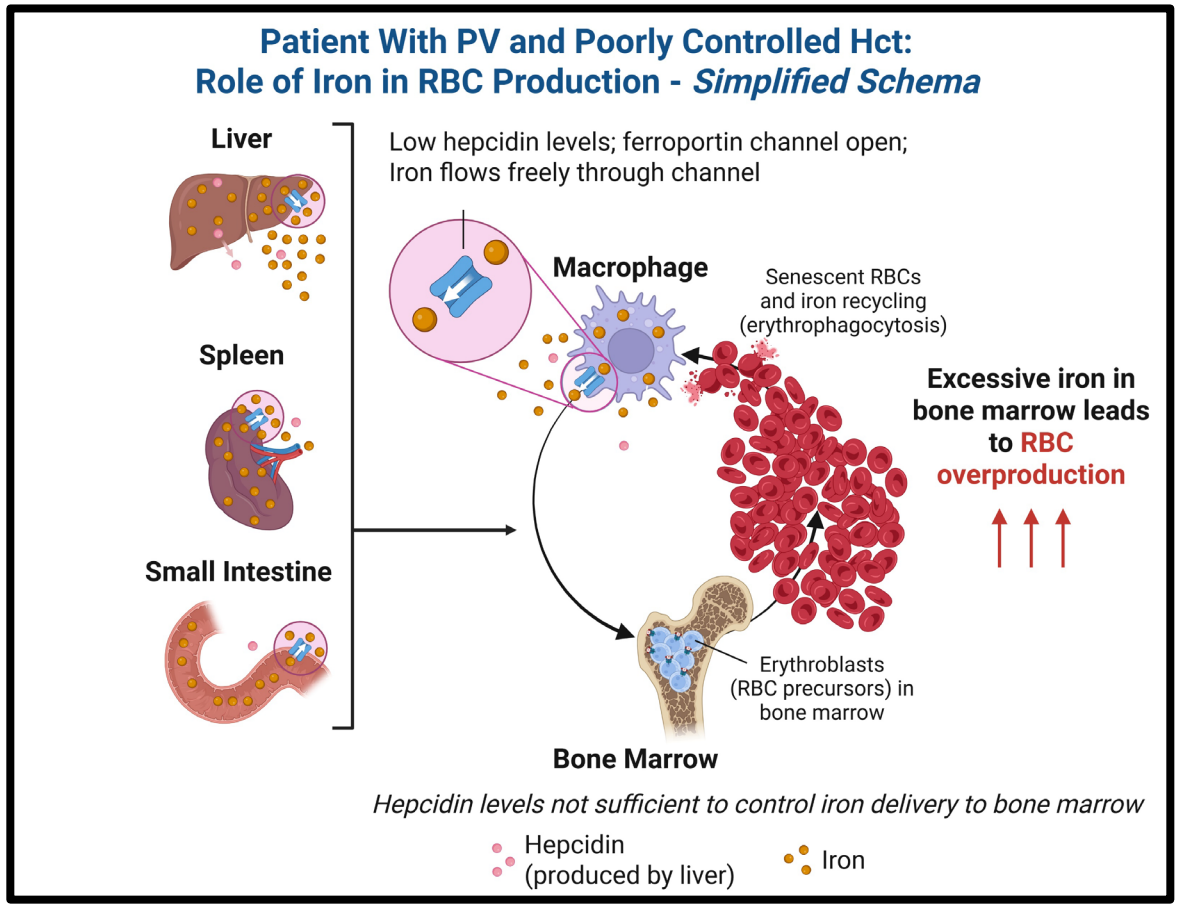
1. Mora B, Passamonti F. *Clin Lymphoma Myeloma Leuk*. 2023;23(2):79-85; 2. Marchioli R, et al. *N Engl J Med.* 2013;368(1):22-33; 3. Tremblay D, et al. *JAMA.* 2025;333(2):153-60; 4. Alvarez-Larrán A, et al. *Haematologica.* 2016;102(1):103-9; 5. Verstovsek S, et al. Ann Hematol. 2023;102(3):571-81. 6. Ginzburg YZ, *Leukemia*. 2018;32(10):2105-16.

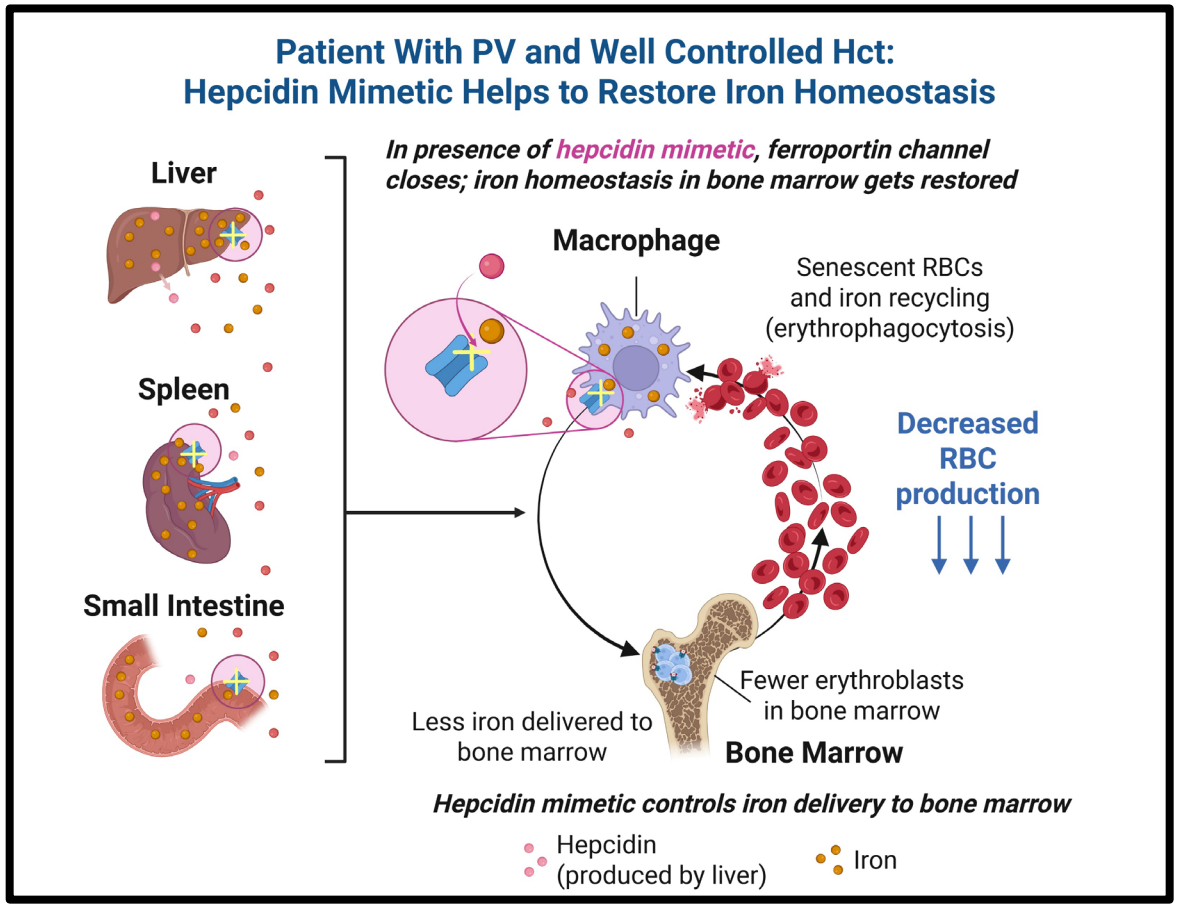


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Polycythemia Vera and the Role of Iron and Hepcidin in Red Blood Cell Production






Images created in BioRender. (2025) https://BioRender.com/y23e071

# Rusfertide in Polycythemia Vera (PV)



- Rusfertide is a first-in-class subcutaneous peptide mimetic of the endogenous hormone hepcidin, the principal regulator of iron homeostasis
- In the phase 2 REVIVE study (NCT04057040), rusfertide met the primary endpoint for response (ie, Hct control and absence of PHL eligibility) in patients with PV[1]
- VERIFY (NCT05210790) is a global, ongoing phase 3 study designed to confirm the benefit of adding rusfertide to current standard-of-care (CSC) therapy vs placebo with CSC in patients with PV who require frequent phlebotomies

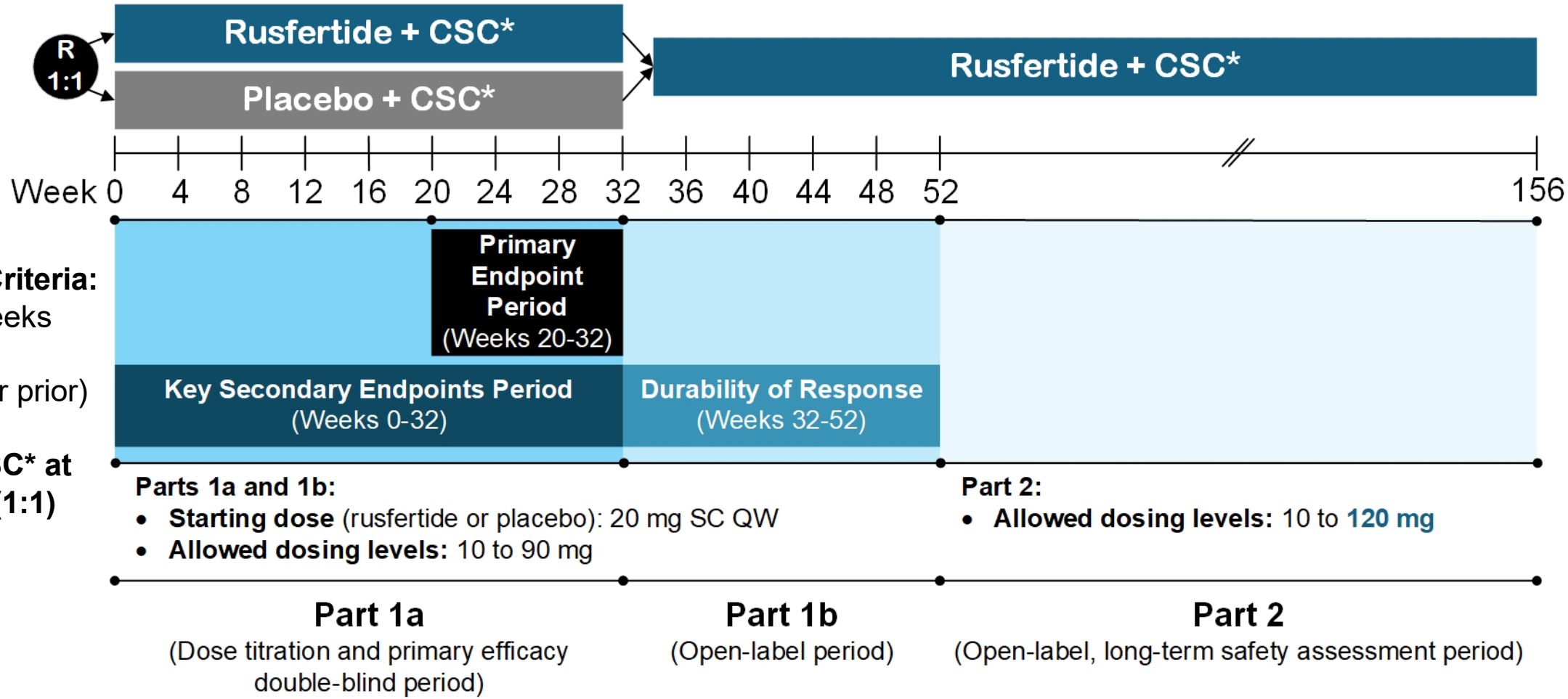
1. Kremyanskaya M, et al. *N Engl J Med*. 2024;390(8):723-35.
Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

# Phase 3 VERIFY Study (NCT05210790) Design in PV



**Key Inclusion Criteria:**
- ≥3 PHL (28 weeks prior) OR
- ≥5 PHL (1 year prior)

**Stratified by CSC* at randomization (1:1)**




*PHL ± CRT

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera; QW, once-weekly; R, randomization; SC, subcutaneous.



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Phase 3 VERIFY Study (NCT05210790) in PV
## *Prespecified Primary and Key Secondary Endpoints*



### Rusfertide with CSC vs placebo with CSC:

- **Primary endpoint (US FDA):** Weeks 20-32
  - Clinical response (absence of phlebotomy eligibility, ie, confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%)

- **Key secondary endpoints:** Weeks 0-32
  - Mean number of phlebotomies (EU EMA)
  - Proportion of patients with Hct <45%
  - Mean change from baseline in PROMIS Fatigue SF-8a Score
  - Mean change from baseline in MFSAF TSS7

EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; Hct, hematocrit; MFSAF TSS, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score; PROMIS, Patient-Reported Outcomes Measurement Information System; PV, polycythemia vera; SF, short form.


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Baseline Demographics and Disease Characteristics



| | 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



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# 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 Inhibitor** | | | |
| Ruxolitinib | 3 (2.1) | 5 (3.4) | 8 (2.7) |

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

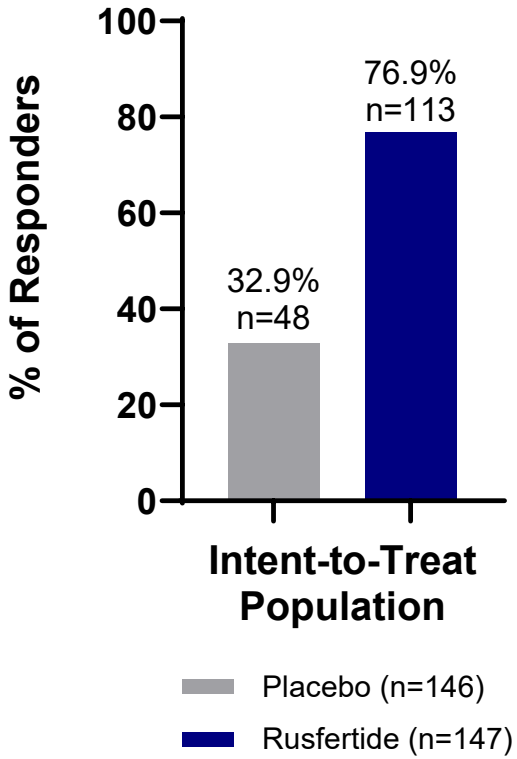
Data cutoff: 7 January 2025

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



| | 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) |

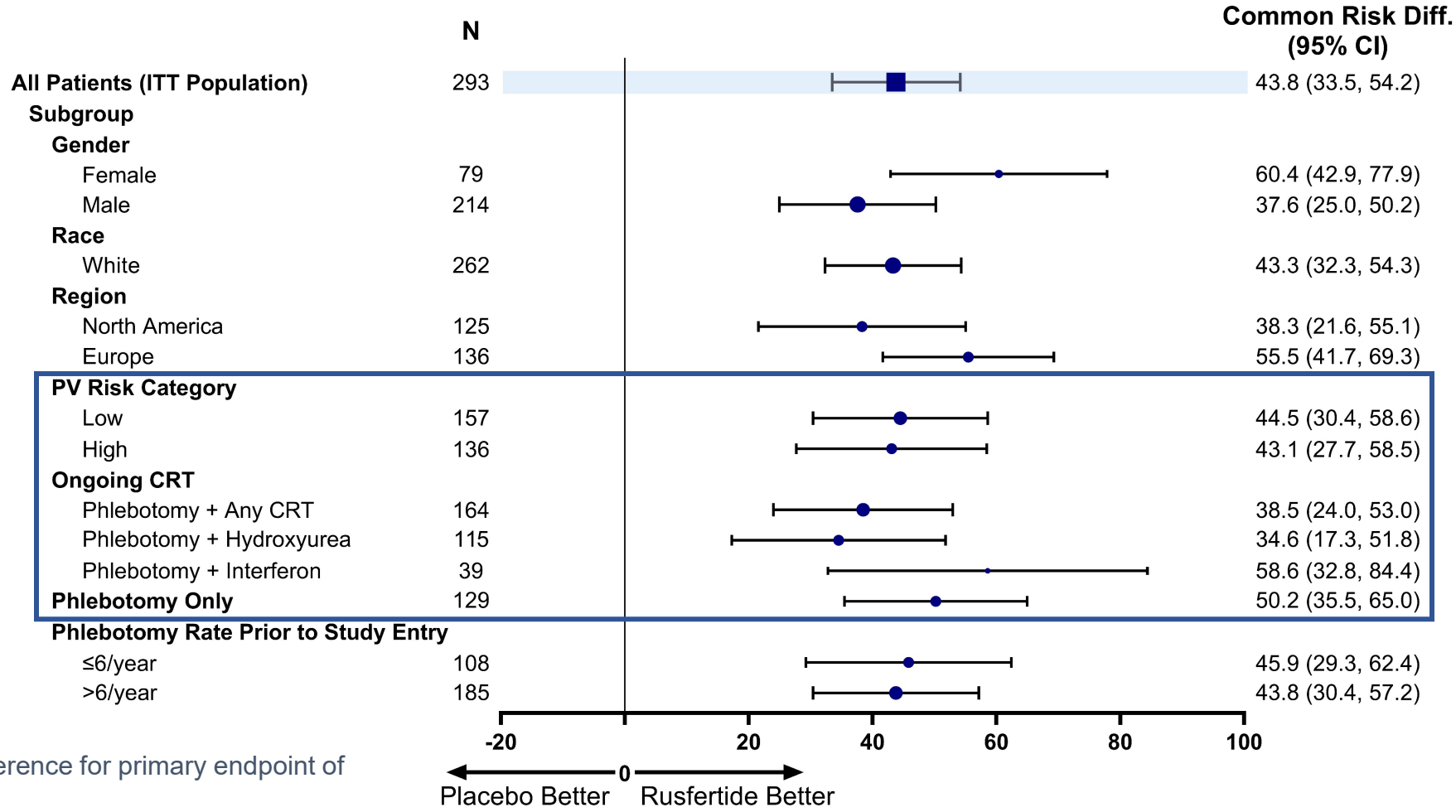
[a]Responder = absence of phlebotomy eligibility (confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%), no phlebotomies, and completion of Part 1a.
*p-value based on Cochran-Mantel-Haenszel test.
Hct, hematocrit.




Data cutoff: 7 January 2025

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






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

Data cutoff: 7 January 2025

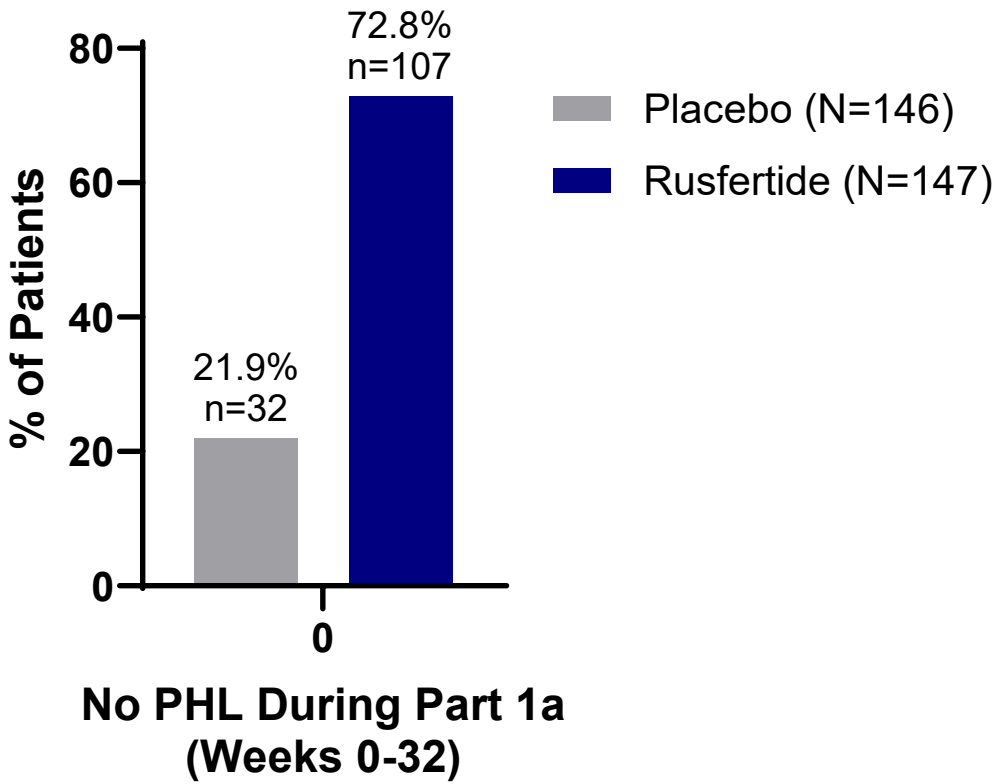

PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Rusfertide + CSC Reduced the Mean Number of PHL From Weeks 0-32 vs Placebo + CSC (p<0.0001): *Key Secondary Endpoint #1*



| Number of Phlebotomies | Placebo + CSC (n=146) | Rusfertide + CSC (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.




- 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

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera.

Data cutoff: 7 January 2025



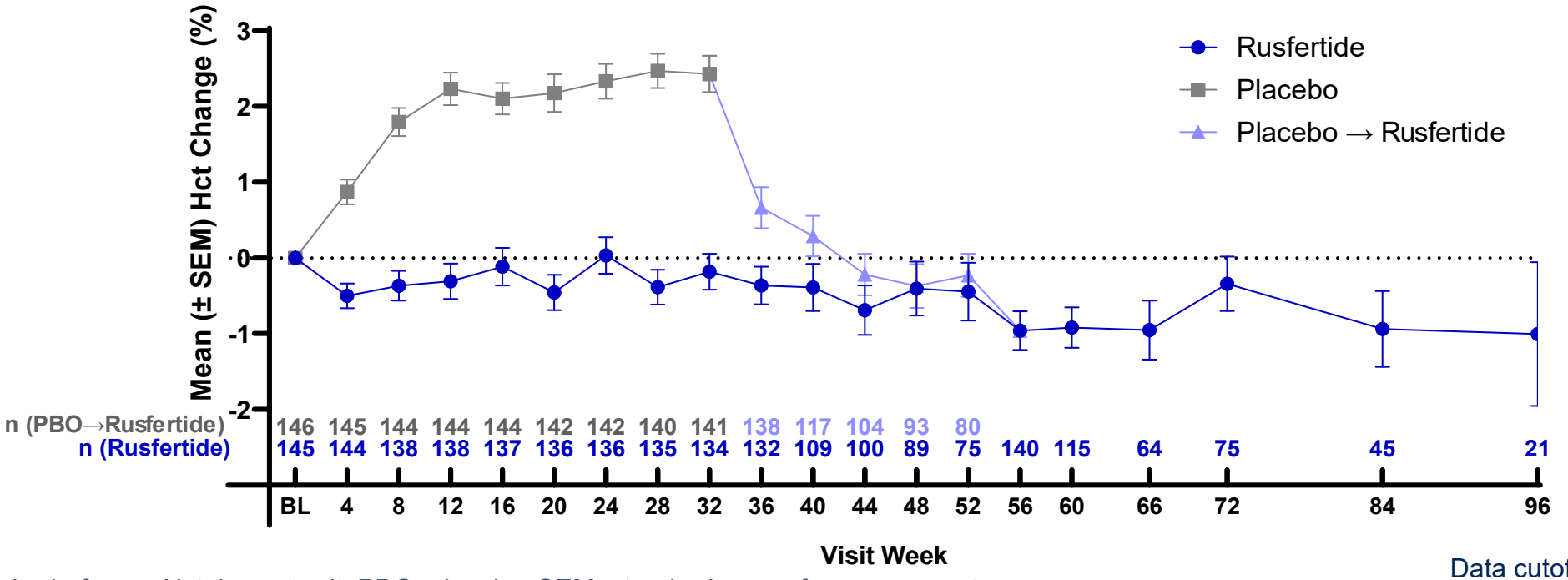
PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Rusfertide + CSC More Likely to Maintain Hct <45% From Weeks 0-32 vs Placebo + CSC: *Key Secondary Endpoint #2*



| | Placebo + CSC (n=146) | Rusfertide + CSC (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.




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

Data cutoff: 7 January 2025

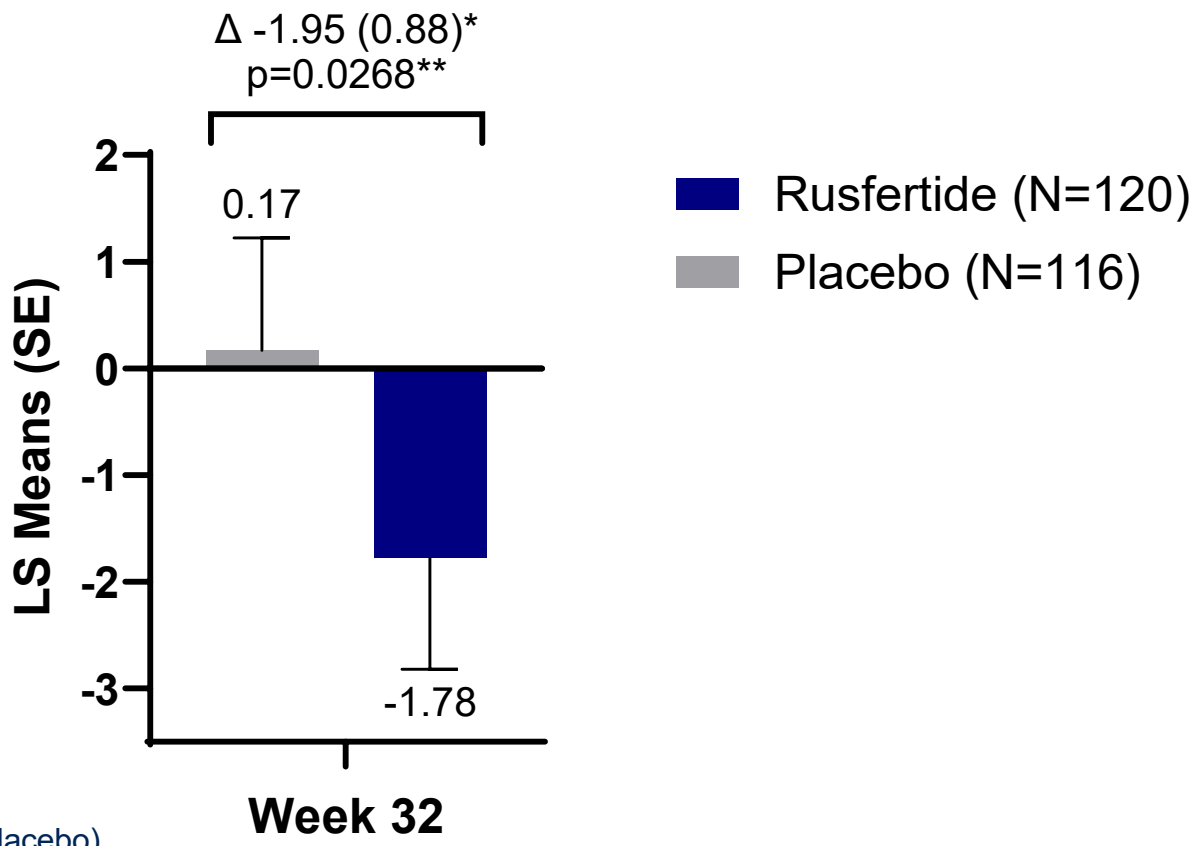


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Rusfertide Demonstrated an Improvement in the PROMIS Fatigue SF-8a Total T-Score at Week 32 vs. Placebo: *Key Secondary Endpoint #3*



## LS Means Difference at Week 32:




*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.

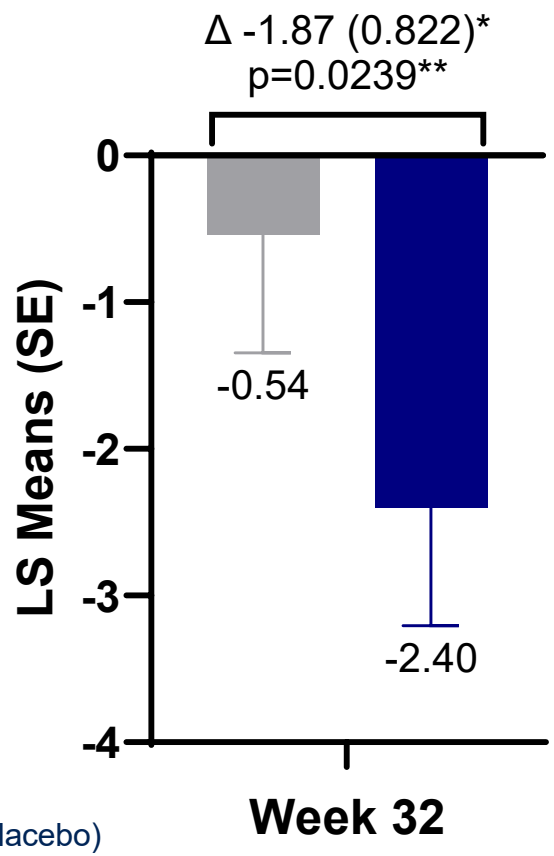
Data cutoff: 7 January 2025


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Rusfertide Demonstrated an Improvement in the MFSAF TSS7 at Week 32 vs. Placebo: *Key Secondary Endpoint #4*



## LS Means Difference at Week 32:




Rusfertide (N=126)

Placebo (N=125)

- 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.


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# 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 + CSC (n=146) | Rusfertide + CSC (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) |

*Safety analysis set.
AE, adverse event; CSC, current standard-of-care; TEAE, treatment-emergent adverse event.

[a]Injection site reactions (grouped term); all other TEAEs are preferred terms.

Data cutoff: 7 January 2025



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# 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 + CSC (n=146) | Rusfertide + CSC (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.
AE, adverse event; MI, myocardial infarction; TE, thromboembolic event; TEAE, treatment-emergent adverse event.

Data cutoff: 7 January 2025


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Conclusions



- Rusfertide is an investigational weekly subcutaneous injection for PV
- In the phase 3 VERIFY study that included patients with PV who were receiving CSC, rusfertide met its primary endpoint and all four key secondary endpoints vs. placebo
  - In VERIFY Part 1a, rusfertide:
    - Significantly reduced the PHL eligibility and improved Hct vs. placebo
    - Demonstrated a statistically significant improvement in symptoms (assessed using two PRO instruments)
- Rusfertide demonstrated a manageable 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

CRT, cytoreductive therapy; CSC, current standard-of-care; Hct, hematocrit; PHL, phlebotomy; PRO, patient-reported outcome; PV, polycythemia vera.

# Agenda

## Today's Topics

**Efficacy and Safety Results from the Ph3 Trial of Rusfertide in PV Patients**

**P.K. Morrow**
*Head of Oncology Therapeutic Area Unit*

**Market Opportunity**

**Teresa Bitetti**
*President, Global Oncology Business Unit*

**Q&A Session**

**Panelists**

**P.K. Morrow**
*Head of Oncology Therapeutic Area Unit*

**Teresa Bitetti**
*President, Global Oncology Business Unit*

# PV patient journey highlights unmet need in current treatment paradigm as patients cycle through options with inconsistent HCT and tolerability

## Presentation and Diagnosis

**Initial Presentation:** Routine blood work or thrombotic event

**Work Up:** **Blood tests** prompt a referral to Hematology/Oncologist

**Diagnosis:** Hem/Onc diagnoses PV and assesses risk

## Initial Treatment and Management

**Immediate:** Phlebotomy (PHL) after diagnosis

- **LOW RISK: Regular PHL** to reduce HCT
  - PHL inconsistently, temporarily reduces HCT
  - PHL results in iron deficiency; amplifies PV symptoms
- **HIGH RISK: PHL with HU or Interferon** if PHL alone is insufficient

*"I don't love phlebotomy. Most patients hate it. It's exchanging PV for symptomatic iron deficiency…nobody can sustain that."*

***- MPN Specialist***

## Cycling on through treatments

2L/3L options often **add-on to PHL**

- **Introduces 2L/3L treatments if** not controlled and/or patient QoL is unmangable
- **2L HU** an off-label[1] cytoreductive chemotherapy
- **Ruxolitinib or Ropeg-interferon** added for HCT control or tolerability and/or based on HCP preference

Current 2L+ therapies may have side effects and *safety* concerns

*"There's **side effects that make HU impossible to take for some patients**…30% of patients drop off."*

***- MPN Specialist***

## Ongoing Management

Monitor blood counts and treatment side effects

Adjusts treatment as necessary



*Recommended threshold levels for hematocrit = 45% in men and 42% in women

1. HU is an off-label treatment in the US

# Rusfertide aims to deliver rapid, consistent & sustained HCT control and is expected to be used at each step of the treatment landscape

**~155k diagnosed** patients in the US with **~78K treated**

Patients are often on polytherapy and will cycle through various treatments

**~41K** Phlebotomy (PHL) And/Or **~26K** Hydroxy Urea (HU) And/Or **~6K** Ruxolitinib And/Or **~3K** Ropeg-interferon

**Unmet needs exist at each step of the treatment landscape, with potential for rusfertide to reach up to 10% of the treated population.**

Driving awareness of the unmet needs in PV › Working broad access and inclusion in guidelines › Engaging with key stakeholders to promote use of Rusfertide ‹› Exploring digital solutions for optimal patient onboarding

**Rusfertide may provide consistent hematocrit control and reduce treatment burden to achieve peak revenue potential of $1-2B**



Source: Komodo Health closed claims dataset (2016-2023); Note: ~2,000 patients are treated via a combination of other therapies; Please refer to the Important Notice at the start of this presentation for more information about peak revenue estimates.

# Rusfertide has the potential to be a new standard of care in PV based on Ph3 data

## Treatment Goals

Consistently maintaining HCT<45%
- Uncontrolled HCT is associated with ~4x higher risk of death from cardiovascular causes or thrombotic events[2]

Reduce burden of phlebotomies
- PHLs results in iron deficiency and amplifies PV symptoms

Reduce treatment/symptom burden
- 84% of patients report fatigue, and 23% report spending full days in bed because of symptoms[3]

Deliver efficacy independent of current background treatment

## Emerging Rusfertide Profile[1]

- ✓ **63%** of patients maintained HCT<45% vs 14% placebo
- ✓ **77%** of patients didn't need a PHL in wks 20-32
- ✓ **>3x LESS** mean number of PHL wks 0-32 vs placebo
- ✓ Both PRO endpoints met with statistically significance
- ✓ Generally well tolerated safety profile with a majority of TEAEs being mild or moderate
- ✓ Demonstrated efficacy against placebo + background SOC including, PHL, HU, JAK and interferon

1. Target profile based on Ph3 data
2. Aaron T. Gerds, Ruben Mesa, John M. Burke, Michael R. Grunwald, Brady L. Stein, Peg Squier, Jingbo Yu, J. E. Hamer-Maansson, and Stephen T. Oh. Association between elevated white blood cell counts and thrombotic events in polycythemia vera: analysis from REVEAL. Blood. 1646 18 APRIL 2024 | VOLUME 143, NUMBER 16
3. Mesa R, et al. *BMC Cancer* 2016;16,167

# Unlocking full potential of rusfertide for patients with PV

***Potential to provide rapid, consistent & sustained hematocrit control with a manageable safety profile***

Approximately 155,000 patients diagnosed with PV in US with only 78,000 currently on treatment

Hematocrit control (<45%) is primary treatment goal of physicians for PV, HCT ≥45% increases risk of thrombotic event and cardiovascular events

78% of patients remain uncontrolled with HCT cycling above 45% in-between treatments

Current treatment options can exacerbate PV symptoms and/or cause significant side effects

VERIFY study met all endpoints with 77% of patients no longer eligible for phlebotomy and a manageable safety profile

The addition of rusfertide to on-going therapy represents a potential new standard of care for patients with PV and peak revenue potential of $1-2B

# Agenda

## Today's Topics

**Efficacy and Safety Results from the Ph3 Trial of Rusfertide in PV Patients**

**P.K. Morrow**
*Head of Oncology Therapeutic Area Unit*

**Market Opportunity**

**Teresa Bitetti**
*President, Global Oncology Business Unit*

**Q&A Session**

**Panelists**

**P.K. Morrow**
*Head of Oncology Therapeutic Area Unit*

**Teresa Bitetti**
*President, Global Oncology Business Unit*

# Medical Presentation as presented at ASCO 2025

2025 ASCO ANNUAL MEETING

# Results From VERIFY, a Phase 3, Double-Blind, Placebo (PBO)-Controlled Study of Rusfertide for Treatment of Polycythemia Vera (PV)

**Andrew T. Kuykendall**[1], Naveen Pemmaraju[2], Kristen Pettit[3], Joseph Shatzel[4], Alessandro Lucchesi[5], Valentín García-Guitérrez[6], Jiri Mayer[7], Abdulraheem Yacoub[8], Harinder Gill[9], Antonin Hlusi[10], Daniel Sasca[11], Joseph M. Scandura[12], Marina Kremyanskaya[13], Phil Dinh[14], Sarita Khanna[14], Suneel Gupta[14], Arturo Molina[14], Aniket Bankar[15] on behalf of the VERIFY Investigators

[1]Moffitt Cancer Center, Tampa, FL, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]University of Michigan, Ann Arbor, MI, USA; [4]Oregon Health & Science University, Portland, Oregon, USA; [5]IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy; [6]Hospital Universitario Instituto Ramón y Cajal de Investigación Sanitaria, Universidad de Alcalá, Madrid, Spain; [7]University Hospital and Masaryk University, Brno, Czech Republic; [8]University of Kansas Cancer Center, Westwood, Kansas, USA; [9]Department of Medicine, School of Clinical Medicine, LKS Faculty of Medicine, the University of Hong Kong, Hong Kong; [10]Palacky University and University Hospital Olomouc, Olomouc, Czech Republic; [11]Universitaetsmedizin der Johannes Gutenberg - Universitaet Mainz, Mainz, Germany; [12]New York Presbyterian Hospital/Weill Cornell Medical Center, New York, NY, USA; [13]Mount Sinai Medical Center, New York, NY, USA; [14]Protagonist Therapeutics, Inc., Newark, California, USA; [15]Princess Margaret Cancer Centre, Toronto, ON, Canada.



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Key Takeaway Points/Conclusions

1

Phase 3 VERIFY study compared the hepcidin mimetic rusfertide to placebo (each added to current standard-of-care) in patients with polycythemia vera

2

Rusfertide met its primary endpoint, all key secondary endpoints, and had a manageable safety profile consistent with prior studies

3

Rusfertide led to statistically significant improvements in several patient reported outcome measures

# Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm driven by acquired *JAK2* mutations[1-3]
- PV is characterized by excessive production of blood cells which contributes to an increased risk of cardiovascular and thrombotic events
- Primary goal of PV treatment aims to reduce thrombotic risk by achieving and maintaining Hct <45%[2,3]
- Current standard-of-care for PV: phlebotomy ± cytoreductive therapy
- Frequent phlebotomy is burdensome and often insufficient for durable Hct control <45%[4-6]

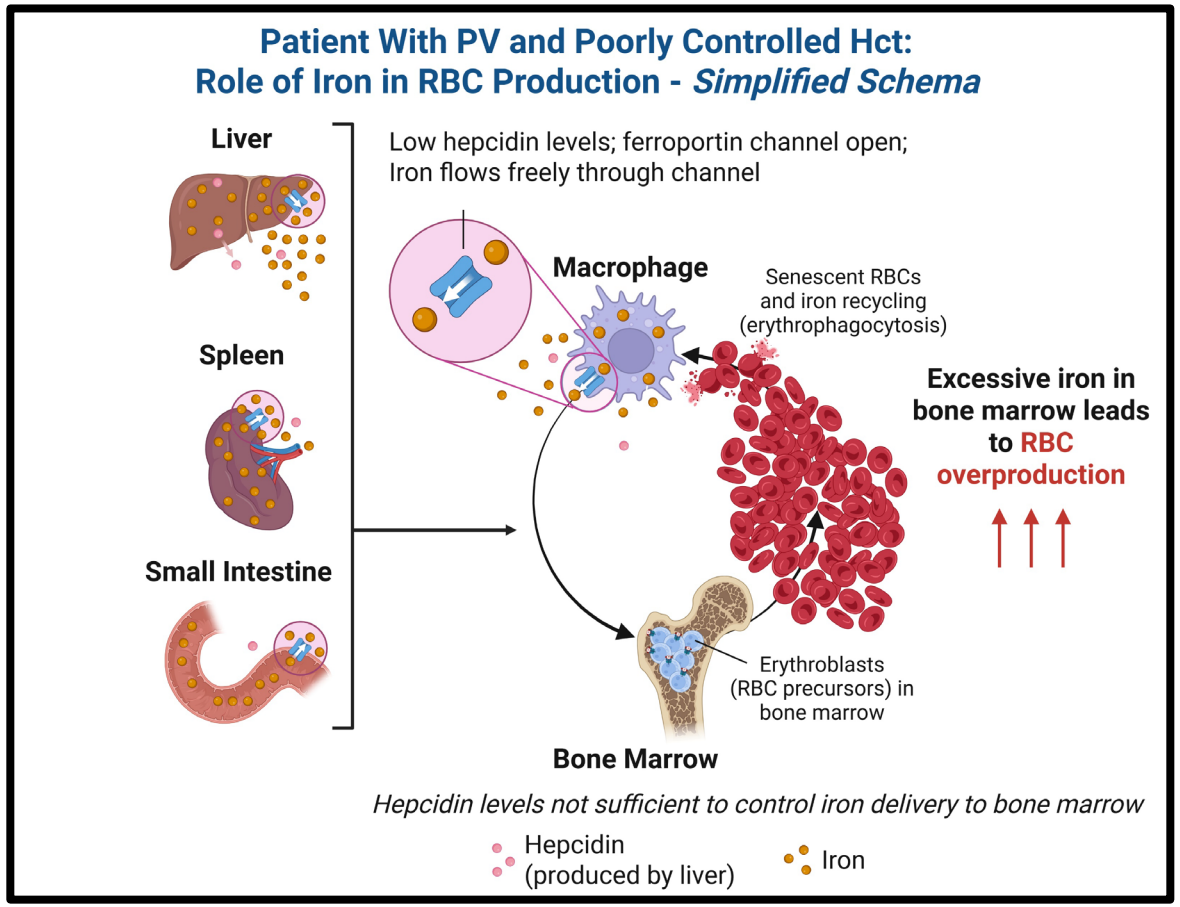
Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

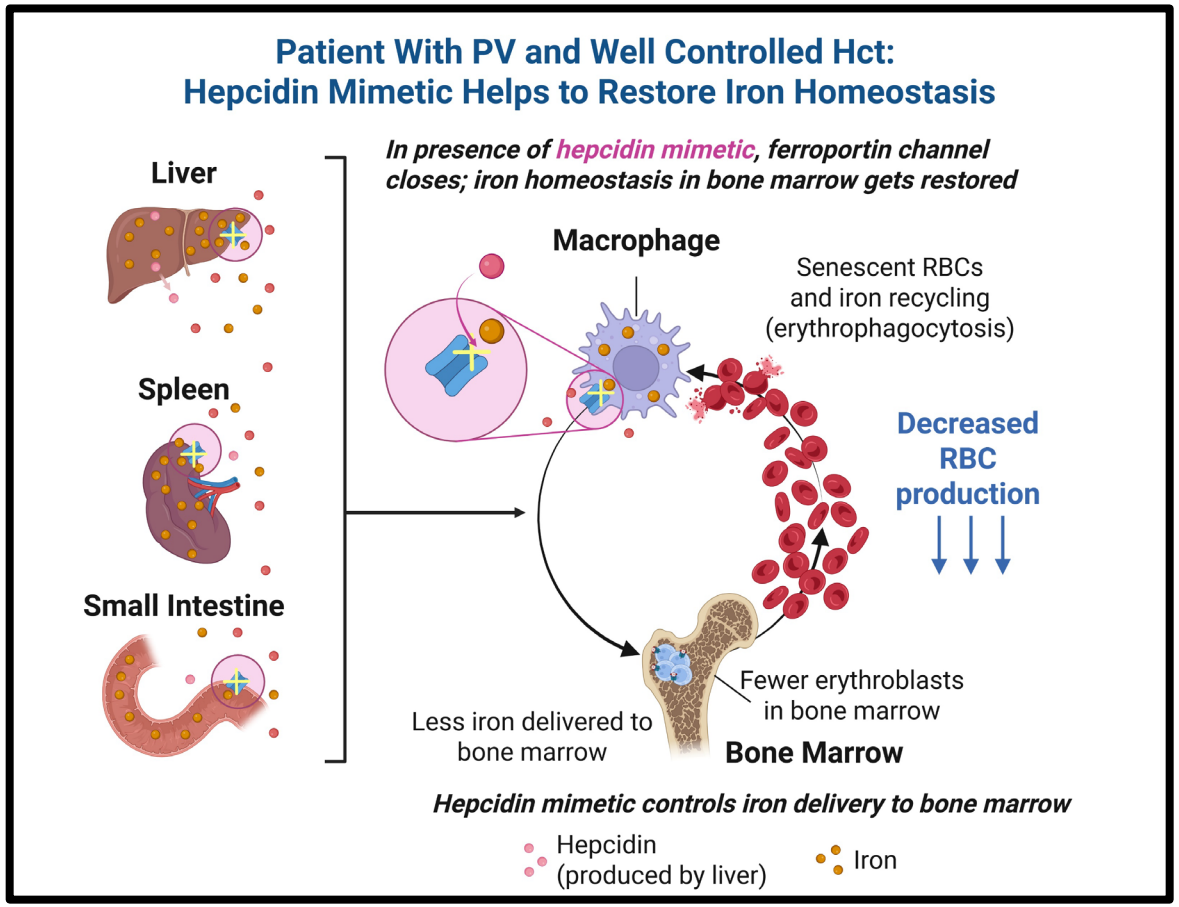
1. Mora B, Passamonti F. *Clin Lymphoma Myeloma Leuk*. 2023;23(2):79-85; 2. Marchioli R, et al. *N Engl J Med.* 2013;368(1):22-33; 3. Tremblay D, et al. *JAMA.* 2025;333(2):153-60; 4. Alvarez-Larrán A, et al. *Haematologica.* 2016;102(1):103-9; 5. Verstovsek S, et al. Ann Hematol. 2023;102(3):571-81. 6. Ginzburg YZ, *Leukemia*. 2018;32(10):2105-16.



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Polycythemia Vera and the Role of Iron and Hepcidin in Red Blood Cell Production



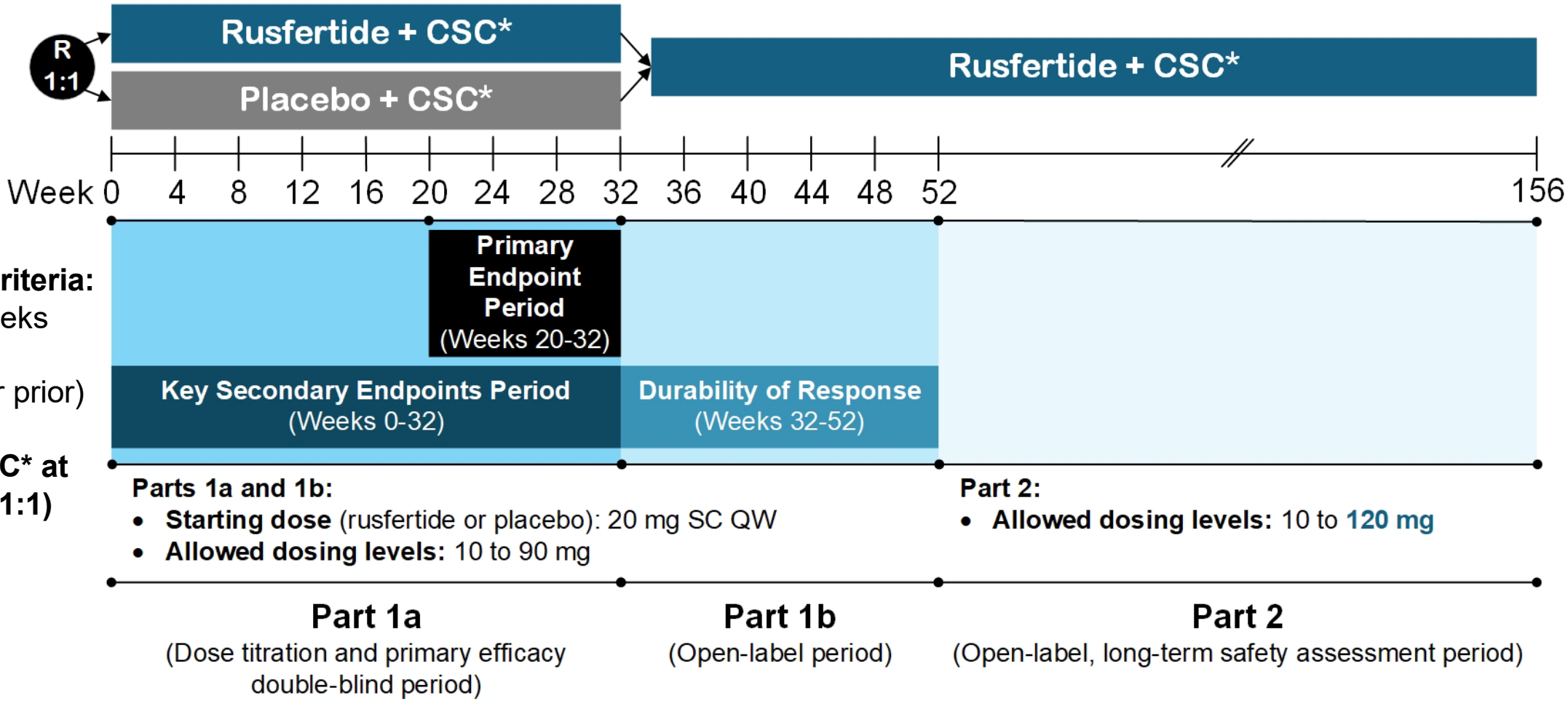

Images created in BioRender. (2025) https://BioRender.com/y23e071

# Rusfertide in Polycythemia Vera (PV)

- Rusfertide is a first-in-class subcutaneous peptide mimetic of the endogenous hormone hepcidin, the principal regulator of iron homeostasis
- In the phase 2 REVIVE study (NCT04057040), rusfertide met the primary endpoint for response (ie, Hct control and absence of PHL eligibility) in patients with PV[1]
- VERIFY (NCT05210790) is a global, ongoing phase 3 study designed to confirm the benefit of adding rusfertide to current standard-of-care (CSC) therapy vs placebo with CSC in patients with PV who require frequent phlebotomies

1. Kremyanskaya M, et al. *N Engl J Med*. 2024;390(8):723-35.
Hct, hematocrit; PHL, phlebotomy; PV, polycythemia vera.

# Phase 3 VERIFY Study (NCT05210790) Design in PV




**Key Inclusion Criteria:**
- ≥3 PHL (28 weeks prior) OR
- ≥5 PHL (1 year prior)

**Stratified by CSC* at randomization (1:1)**

*PHL ± CRT

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera; QW, once-weekly; R, randomization; SC, subcutaneous.


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Phase 3 VERIFY Study (NCT05210790) in PV

*Prespecified Primary and Key Secondary Endpoints*

## Rusfertide with CSC vs placebo with CSC:

- **Primary endpoint (US FDA):** Weeks 20-32
  - Clinical response (absence of phlebotomy eligibility, ie, confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%)

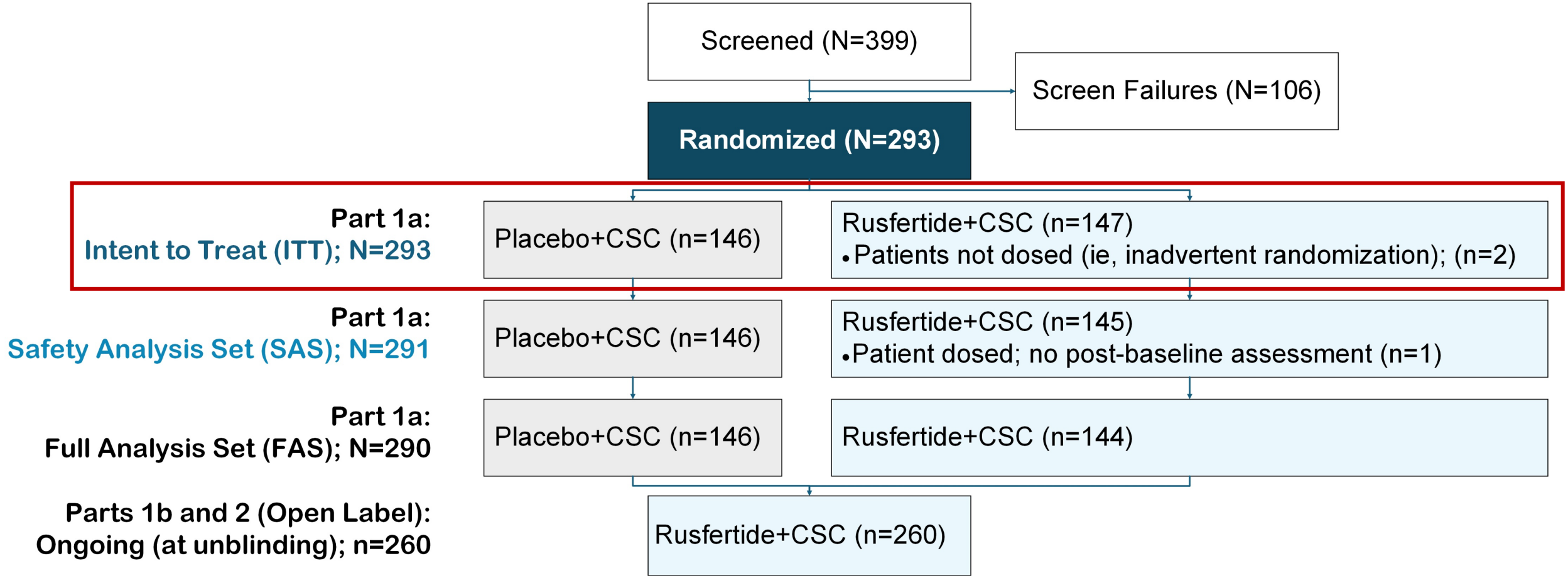
- **Key secondary endpoints:** Weeks 0-32
  - Mean number of phlebotomies (EU EMA)
  - Proportion of patients with Hct <45%
  - Mean change from baseline in PROMIS Fatigue SF-8a Score
  - Mean change from baseline in MFSAF TSS7

EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; Hct, hematocrit; MFSAF TSS, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score; PROMIS, Patient-Reported Outcomes Measurement Information System; PV, polycythemia vera; SF, short form.



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# VERIFY Patient Disposition and Analysis Sets: Part 1a




FAS, all randomized patients according to the treatment assigned at randomization (ITT principle) who received at least one dose of study drug and had a baseline and at least one postbaseline assessment in Part 1a. CSC, current standard-of-care.

Data cutoff: 7 January 2025

# Baseline Demographics and Disease Characteristics

| | 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



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# 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 Inhibitor** | | | |
| Ruxolitinib | 3 (2.1) | 5 (3.4) | 8 (2.7) |

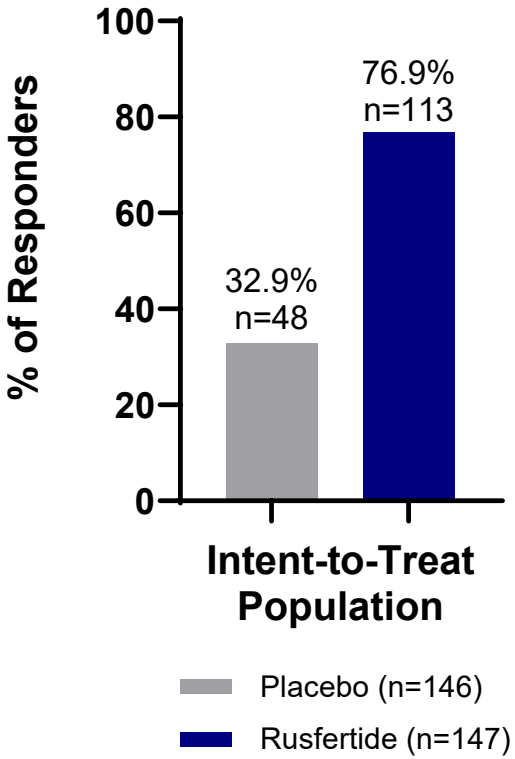
CSC, current standard-of-care; JAK, Janus Kinase.

Data cutoff: 7 January 2025

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

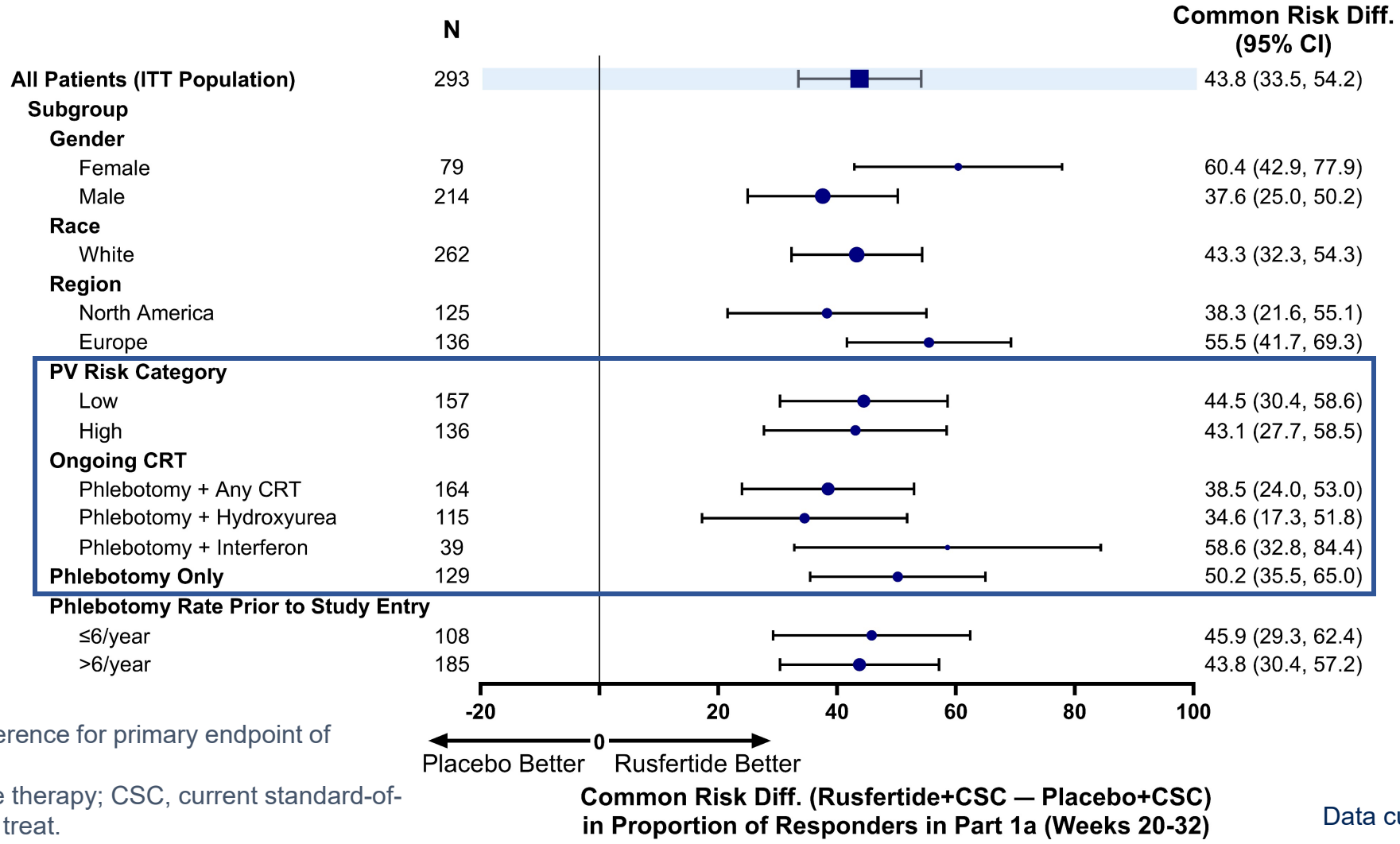
| | Placebo + CSC (n=146) | Rusfertide + CSC (n=147) |
|---|---|---|
| **Responders, n (%)[a]** | 48 (32.9) | 113 (76.9) |
| p-value* | | **<0.0001** |
| **Non-responders, n (%)** | 98 (67.1) | 34 (23.1) |

[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.




Data cutoff: 7 January 2025

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




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

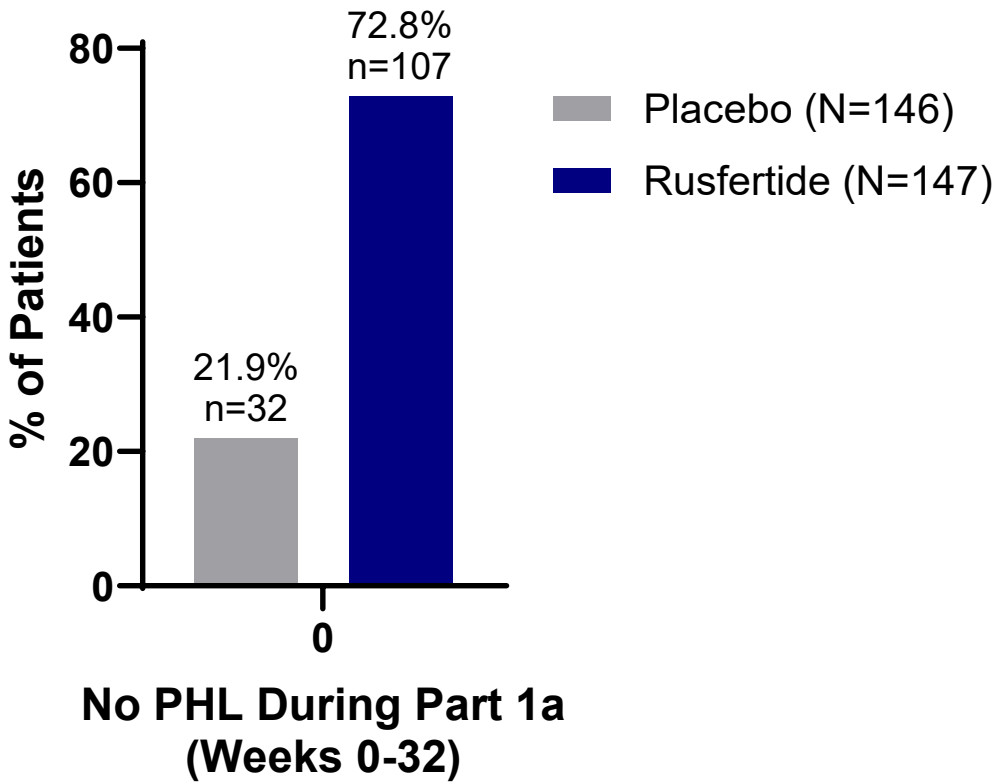
Data cutoff: 7 January 2025


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Rusfertide + CSC Reduced the Mean Number of PHL From Weeks 0-32 vs Placebo + CSC (p<0.0001): *Key Secondary Endpoint #1*

| Number of Phlebotomies | Placebo + CSC (n=146) | Rusfertide + CSC (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.




- 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

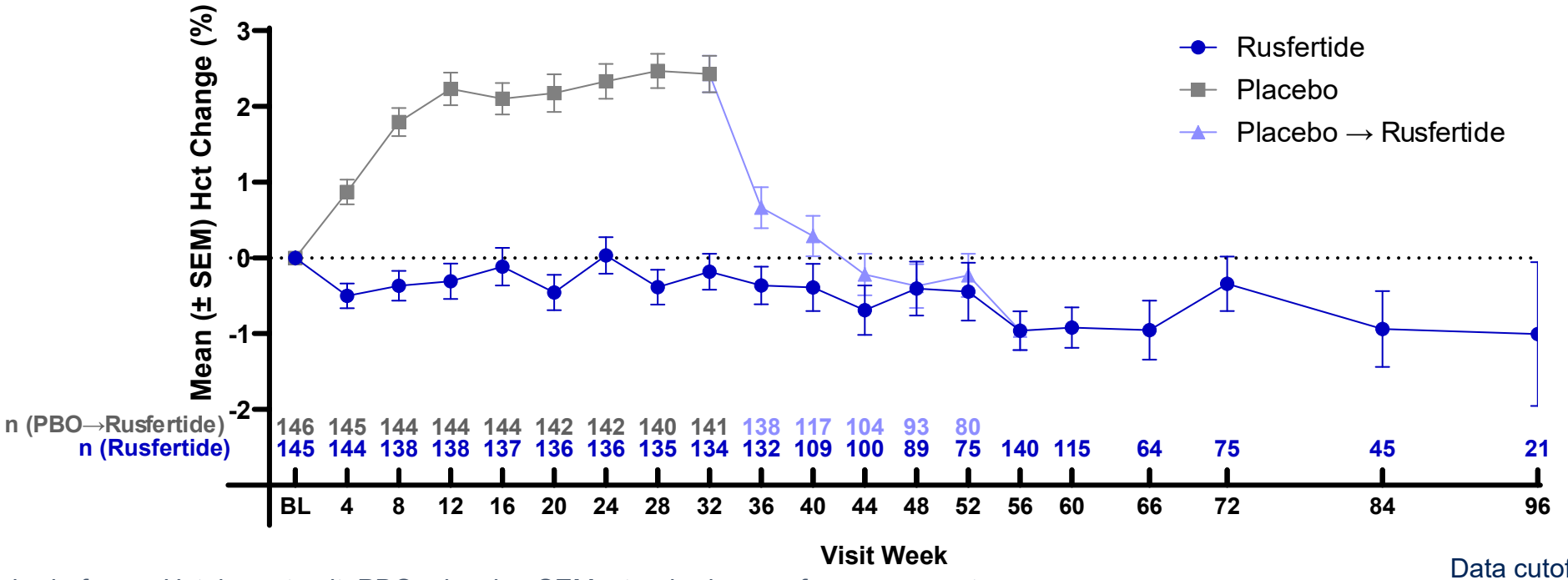
CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera.

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 + CSC (n=146) | Rusfertide + CSC (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.



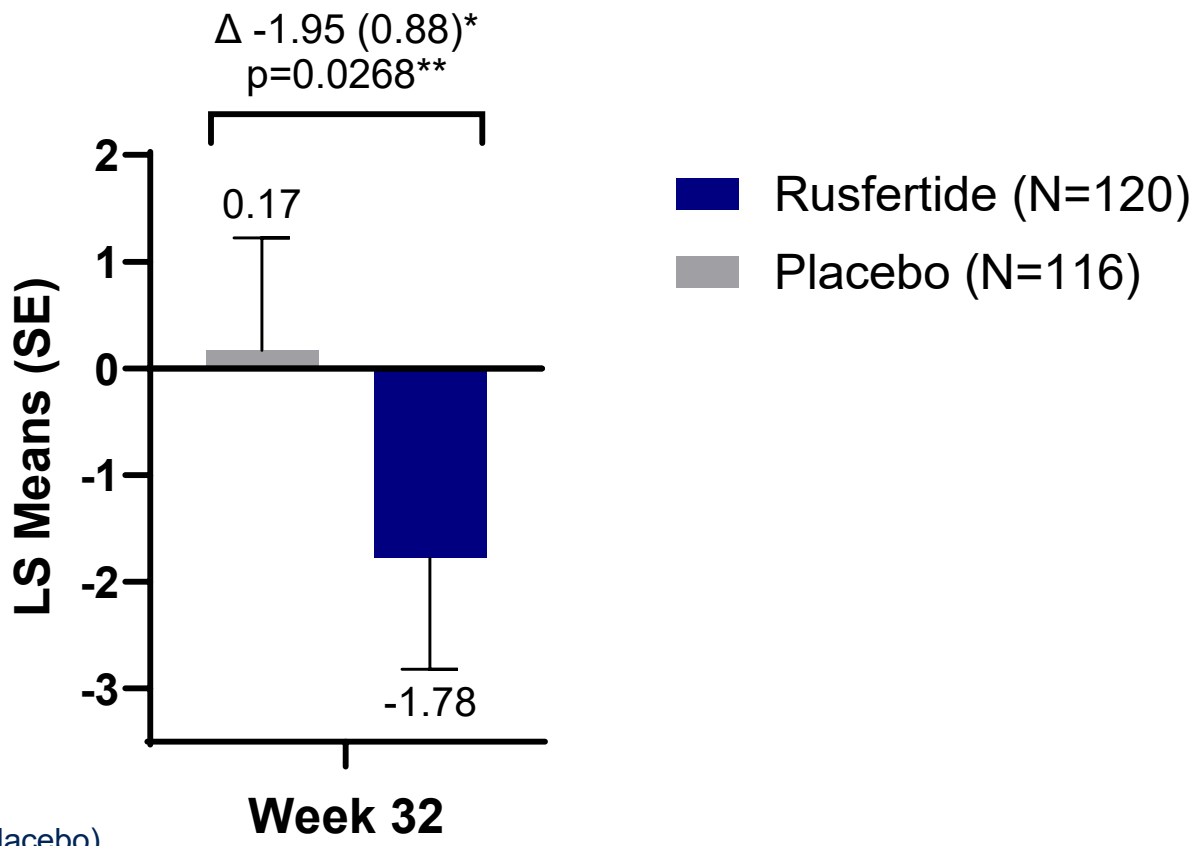

CSC, current standard-of-care; Hct, hematocrit; PBO, placebo; SEM, standard error of measurement.

Data cutoff: 7 January 2025


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Rusfertide Demonstrated an Improvement in the PROMIS Fatigue SF-8a Total T-Score at Week 32 vs. Placebo: *Key Secondary Endpoint #3*

## LS Means Difference at Week 32:

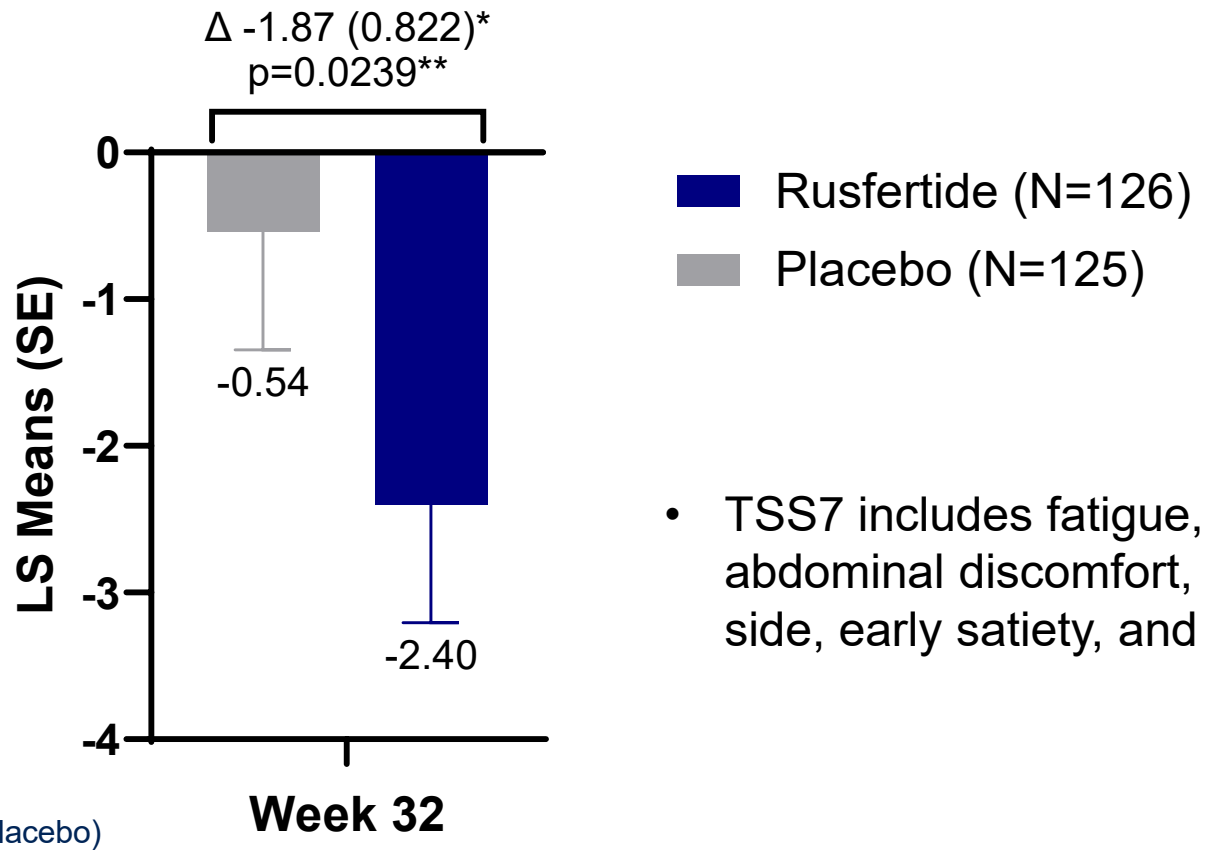



*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error; SF, short form.

Data cutoff: 7 January 2025

# Rusfertide Demonstrated an Improvement in the MFSAF TSS7 at Week 32 vs. Placebo: *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.

# 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 + CSC (n=146) | Rusfertide + CSC (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) |

[a]Injection site reactions (grouped term); all other TEAEs are preferred terms.

*Safety analysis set.
AE, adverse event; CSC, current standard-of-care; TEAE, treatment-emergent adverse event.

Data cutoff: 7 January 2025



PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# 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 + CSC (n=146) | Rusfertide + CSC (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.
AE, adverse event; MI, myocardial infarction; TE, thromboembolic event; TEAE, treatment-emergent adverse event.

Data cutoff: 7 January 2025


PRESENTED BY: Andrew T. Kuykendall, MD (Associate Member, Dept. of Malignant Hematology, Moffitt Cancer Center)

# Limitations

- Heterogeneous patient population that may make interpretability of some of the secondary endpoints (eg, PROs) challenging
- The placebo-controlled portion of VERIFY (Part 1a) was only 32 weeks long
  - Long-term assessment of safety, thrombotic events, and disease transformation or progression is therefore limited and will continue for up to three years (Parts 1b and 2)

PRO, patient-reported outcome.

# Conclusions

- Rusfertide is an investigational weekly subcutaneous injection for PV
- In the phase 3 VERIFY study that included patients with PV who were receiving CSC, rusfertide met its primary endpoint and all four key secondary endpoints vs. placebo
  - In VERIFY Part 1a, rusfertide:
    - Significantly reduced the PHL eligibility and improved Hct vs. placebo
    - Demonstrated a statistically significant improvement in symptoms (assessed using two PRO instruments)
- Rusfertide demonstrated a manageable 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

CRT, cytoreductive therapy; CSC, current standard-of-care; Hct, hematocrit; PHL, phlebotomy; PRO, patient-reported outcome; PV, polycythemia vera.

# We would like to thank all patients and their caregivers who participated in this study along with all investigators, study staff, and clinical trial sites who contributed to VERIFY


The study was sponsored by Protagonist Therapeutics, Inc. (Newark, CA, USA). Medical writing assistance was provided by Elizabeth Schoelwer, PharmD, of MedVal Scientific Information Services, LLC (Princeton, NJ, USA), and Peter Morello, Protagonist Therapeutics, Inc., and was funded by Protagonist Therapeutics, Inc. The study was sponsored by Protagonist Therapeutics, Inc. Protagonist is responsible for development of rusfertide in the U.S. through the completion of the Phase 3 VERIFY trial. Takeda Pharmaceuticals (Cambridge, MA) has rights for rusfertide ex-U.S. development and is responsible for leading global regulatory and commercialization activities.

# Patient Lay Summary Slide

- Rusfertide is an investigational weekly subcutaneous injection for a type of blood cancer called polycythemia vera (PV)
- Patients receiving rusfertide with current standard-of-care therapy saw a reduction in their average number of phlebotomies vs. placebo
  - Red blood cell levels remained within the desired target range (hematocrit <45%)
- Rusfertide was well tolerated and had a safety profile consistent with observations in prior studies
- Rusfertide represents a potential new treatment option for patients with PV