Clinical Study Protocol

NCT Number: NCT05210790

Title: A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300; TAK-121) in Patients with Polycythemia Vera

Study Number: PTG-300-11

Document Version and Date: Amendment 7, 23 Jun 2026

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A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300; TAK-121) in Patients with Polycythemia Vera

Protocol Number: PTG-300-11

Development Phase: Phase 3

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Document Version: Protocol Amendment 7 dated 23 June 2026
Protocol Amendment 6.1 dated 05 June 2025
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Protocol Amendment 5.1 dated 09 January 2025
Protocol Amendment 5 dated 19 November 2024
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Protocol Amendment 3.1 dated 25 July 2023
Protocol Amendment 3 dated 30 June 2023
Protocol Amendment 2 dated 01 November 2022
Protocol Amendment 1 dated 03 December 2021
Original Protocol, 05 November 2021

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SIGNATURE PAGE

Sponsor Signatories:

Electronic signatures of the following individuals are provided on the last page of this document.

[redacted] MD, Clinical Sciences, [redacted]
[redacted] PhD Statistics and Quantitative Sciences (SQS), [redacted]

Medical monitor's and sponsor's responsible medical officer's name and contact information are provided separately in the site manual.

Report SAEs and AESIs within 24 hours, regardless of causal relationship to the investigational product via the email or fax provided in the site manual.

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INVESTIGATOR'S AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and wellbeing of study participants in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 14.4 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Section 17.8.2).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Section 17.8.3 of this protocol.

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Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

Amendment Details

History of Amendments

Ten prior global amendments have occurred, as shown in the table below:

Document	Sponsor Approval Date (dd/mmm/yyyy)	Region
Protocol Amendment 7	23 June 2026	Global
Protocol Amendment 6.1	05 June 2025	Global
Protocol Amendment 6	01 May 2025	Global
Protocol Amendment 5.1	09 January 2025	Global
Protocol Amendment 5	19 November 2024	Global
Protocol Amendment 4	06 September 2024	Global
Protocol Amendment 3.1	25 July 2023	Global
Protocol Amendment 3	30 June 2023	Global
Protocol Amendment 2	01 November 2022	Global
Protocol Amendment 1	03 December 2021	Global
Original Protocol	05 November 2021	Global

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Current Amendment

The table below provides an overview of the current amendment.

Amendment Number:	Amendment 7
Summary of the Amendment	The primary reasons for the amendment are: • To update the nominal rusfertide dose strengths and to simplify the administration instructions to align with the dose delivered in this study. • This update is a labeling/presentation alignment and does not change the rusfertide active ingredient, formulation, or manufacturing process. • To update the sponsor of record to Takeda and incorporate Takeda protocol template administrative/operational sections and policy language.

Summary of Changes in the Current Amendment

Section # and Name	Description of Change	Brief Rationale for Change
Section 1. Title page Section 2. Synopsis Section 5. Introduction Section 7.1. Overall Study Design Section 7.4. Early Trial or Site Closure Section 8. Access to Trial Intervention After End of Trial Section 8.1. Posttrial Access Section 10.3.1 Description of Study Drug Section 11.5 Study Drug Handling and Disposal 14.2.6. Abuse, Misuse, Overdose and Medication Error 14.2.7. Product Complaints 14.3.1 Recording of AEs 14.3.2 Recording of SAEs Section 14.4 Reporting Adverse Events Section 14.6 Emergency Unblinding of Treatment Assignment Section 17.6. Early Site Closure or Trial Termination Section 17.6.1. Decision Rights for Site Closure and Trial Termination Section 17.6.2. Criteria for Early Trial Site Closure Section 17.8.2. List of Investigator Responsibilities	Updated sponsor to Takeda and aligned protocol administrative/operational content with the Takeda R&D Interventional Trial Protocol Template requirements by adding Takeda template sections covering post-trial access, early site closure/trial termination decision rights and criteria, investigator responsibilities and investigator personal-information consent language, and Takeda publication/clinical trial registration and disclosure policy language.	Sponsor change to Takeda requires incorporation of Takeda-mandated protocol template sections/policy language to ensure required governance, participant/site operational clarity (including post-trial access), privacy/data-handling expectations for investigators, and publication/registration/disclosure requirements are documented.

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Section # and Name	Description of Change	Brief Rationale for Change
Section 17.8.3. Investigator Consent to Use of Personal Information Section 18. Publication and Clinical Trial Registration and Disclosure Policies Section 18.1. Publication Policy Section 18.2. Clinical Trial Registration and Disclosure		
Section 1. Title page Section 2. Synopsis Section 5. Introduction	Added text describing name of investigational product.	To add Takeda product name for investigational product.
Section 2. Synopsis Section 9.3.1. Study Stopping Rules	Removed references to Safety Monitoring Committee; clarified that cancer-development event reviews, causality assessment, and stopping boundary decisions are performed by sponsor/medical monitor.	The Safety Management Team approved discontinuation of the Safety Monitoring Committee, which has focused on malignancy risk and consistently supported continuation of the study without changes. Given the mature and comprehensive rusfertide safety database, including a malignancy analyses submitted in the New Dug Application, ongoing oversight by the Safety Monitoring Committee is unlikely to add further value. Safety oversight will remain robust. Patient Safety and Pharmacovigilance will continue routine pharmacovigilance, including monthly signal detection and quarterly Safety Management Team reviews. Cancer events will remain AEs of special interest with expedited reporting and escalation as needed. Given the mature safety dataset and the strength of existing safety governance, disbanding the Safety Monitoring Committee is appropriate at this stage.
Section 2. Synopsis Section 5.2.1 Nonclinical Studies Section 7.2 Rationale for the Study Design Section 10.2 Blinding an Unblinding Section 10.4.1 Study Drug Dosing Section 10.4.1.1.1 Part 1a Section 10.4.1.1.2 Part	Adjusted dose strengths and dosing instructions.	Upon review of the rusfertide manufacturing process and analytical controls, it was identified that the expansion volume of the lyophilized drug product cake was not accounted for during drug product development of the Lyophilized Drug Formulation (LPF). As a result, the product dose strengths are not in line with the originally planned dose strengths. To avoid impacting the existing manufacturing process and controls, the dose strengths are adjusted through back-calculation using the center of the range (target) values used in the clinical studies and accounting for the expansion volume upon

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Section # and Name	Description of Change	Brief Rationale for Change
1b Section 10.4.1.2.1 Part 1a and Part 1b Section 10.4.1.2.2 Part 2 and Part 3 Section 11.1.1 Rusfertide Section 12.2.2 Randomization: Day 1 of Week 0 - First Dose Section 12.2.3 End of Part 1a (Week 32)/Beginning of Part 1b		reconstitution. The adjusted dose strengths are consistent with the actual doses that were administered in the current clinical trial (PTG-300-11).
Section 2 Synopsis Section 7.1.2 Treatment Duration Including Post-Treatment Safety Follow-up Section 12 Study Procedures Section 12.2.5.1 End of Study/Safety Follow-Up Visit for Participants Discontinuing at or Before Week 156 Section 12.2.6.1 End of Study for Part 3 Section 12.2.7 New Cancer Events after Study Completion or Early Termination Section 12.2.8 Early Termination Section 13.2 Adverse Events	Removed text describing new cancer events follow up after Part 3	This update aligns with the plan for long-term follow-up of new cancer events at 6 and 12 months for all participants who discontinued early prior to, or completed, the long-term extension of Part 2 at Week 156. This follow-up is anchored to Part 2 and applies regardless of whether participants entered the additional extension in Part 3. Cancer events will continue to be monitored in Part 3.
Section 5.2.2 Clinical Studies Section 7.2 Rationale for the Study Design	Added text describing formulations used in clinical trials.	To clarify the 2 different formulations used in clinical Trials PTG-300-04 and PTG-300-08 versus PTG-300-11 and PTG-300-21.
Section 5.2.2 Clinical Studies	Added text referring to IB.	To clarify where to find updated data for clinical trials.
Section 5.2.2 Clinical Studies	Updated clinical program study status/tense (completed versus ongoing) and refreshed cumulative enrollment statement; updated REVIVE	To ensure protocol background statements are accurate as of Amendment 7 and to maintain consistent tense aligned with study status.

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Section # and Name	Description of Change	Brief Rationale for Change
	(PTG-300-04) and PACIFIC (PTG-300-08) status language; confirmed VERIFY (PTG-300-11) and THRIVE (PTG-300-21) are ongoing (as applicable).	
Section 5.2.2.1 Clinical Pharmacology of Rusfertide Section 5.2.2.3 Rusfertide Clinical Efficacy in PV Participants (Phase 2 Protocol PTG-300-04) Section 5.2.2.4 Rusfertide Clinical Efficacy in PV Participants (Phase 2 Protocol PTG-300-08) Section 7.2 Rationale for Study Design	Specified dose formulation.	To clarify which formulation was used in the specified clinical trial.
Section 5.2.2.2 Rusfertide Clinical Safety	Updated clinical safety results.	To provide updated safety data.
Section 5.2.4 Benefit/Risk Assessment	Updated text.	To provide updated information concerning risks associated with rusfertide.
Section 7.2 Rationale for Study Design	Specified trial number.	To clarify which trial is being described.
Section 10.4.1 Study Drug Dosing Section 10.4.1.4 Dose Increase for Hematocrit Control Section 10.4.1.5 Dose Decrease	・Revised text describing dose adjustment instructions. ・Added tables for instructions for trial intervention administration, dose escalation, and dose reduction.	To simplify dosing and administration to reflect the adjusted dose strengths; shown in table for clarity.
Section 10.4.2 Rusfertide Dosing in Part 2 and Part 3	Revised text describing dosing rules for Part 2 and Part 3.	To clarify the dosing schedule and allow participants to continue on an already existing flexible dosing regimen in Part 2 and Part 3, as permitted under prior versions of the protocol or protocol amendments, at the investigator's discretion.
Section 10.5.1 Delayed Dosing	Revised text describing procedures for delayed dosing.	To clarify delayed dosing administration in the case of dosing every 2 weeks.
Section 10.7.1 Injection Site Reactions (ISRs)	Removed text describing dose-splitting for ISRs.	To remove text describing the splitting of doses to reduce ISRs, which does not apply in this clinical trial.
Section 11.1.1	Revised text describing	To clarify the nominal injection volume.

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Section # and Name	Description of Change	Brief Rationale for Change
Rusfertide Section 11.1.2 Placebo	injection volume.	

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2. SYNOPSIS

Name of Sponsor/Company: Takeda Development Center Americas, Inc.	
Name of Investigational Product: Rusfertide (also known as PTG-300 or TAK-121)	
Protocol Number: PTG-300-11	**Country:** Multiple
Title of Study: A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300; TAK-121) in Patients with Polycythemia Vera	
Study center(s): Approximately 100 sites	
Phase of development: 3	
Indication: Rusfertide is indicated for the treatment of patients diagnosed with polycythemia vera (PV)	
Objective: To evaluate the safety and efficacy of rusfertide in participants with polycythemia vera (PV) in maintaining hematocrit control.	

Study Design: This is a Phase 3 study in participants with polycythemia vera.

- Part 1a: randomized, double-blind, placebo-controlled, add-on parallel-group period for 32 weeks. Participants will be randomized 1:1 in a blinded fashion to 32 weeks of add-on rusfertide or placebo treatment. Rusfertide or placebo will be added-on to each participant's ongoing therapy for PV. Randomization will be stratified by ongoing PV therapy.
- Part 1b: open-label treatment phase during which all participants who complete Part 1a successfully will receive rusfertide for 20 weeks (Week 32 through Week 52).
- Part 2: long term extension for 104 weeks (Week 52 through Week 156) during which all participants who complete Part 1b will continue to receive rusfertide.
- Part 3: Rusfertide treatment extension for participants who complete Part 2. Participants who complete Part 2 may be eligible for Part 3 if, in the opinion of the investigator, they are continuing to derive benefit from rusfertide and:
  - do not have access on the commercial market following local commercial availability under the standard pricing and reimbursement model in a country

  or

  - cannot obtain rusfertide through a post-trial access (PTA) program.

  During Part 3, participants will come to the clinic every 12 weeks. The dose of cytoreductive agents may be adjusted for either safety or efficacy; additionally, participants may begin new cytoreductive therapy in Part 3.

Weeks 32, 52, and 156 are transition visits between study parts; week ranges are inclusive and refer to the scheduled study week/visit label.

Methodology

SCREENING:

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Participants may be screened for eligibility up to 42 days prior to randomization. Screening will begin when the participant signs the informed consent form. Participants who fail screening may be rescreened once. During screening, a participant may undergo phlebotomies to decrease hematocrit to <45% with the last phlebotomy being 6 days or more prior to randomization.

PART 1a: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, ADD-ON PARALLEL PHASE (Week 0 through Week 32)

All participants must have a hematocrit <45%, white blood cells (WBC) 4000/µL to 20,000/µL and platelets 100,000/µL to 1,000,000/µL at Week 0 prior to randomization. Eligible participants will continue to receive their therapy at screening for PV (phlebotomy alone or cytoreductive therapy+phlebotomy). Participants who meet the eligibility criteria will be stratified by ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other) and randomized 1:1 to treatment with rusfertide or placebo added on to the participant's ongoing PV therapy at Week 0 using Interactive voice randomization (IVR) or Interactive Web Response (IWR) System (IxRS). The starting dose of study drug (rusfertide or placebo) is 19 mg by subcutaneous (SC) injection once a week. The dose should be adjusted to maintain hematocrit <45%. In order to account for day-to-day hematocrit variations ≥45% it is recommended that the dose of study drug (rusfertide or placebo) be increased when hematocrit ≥43% or the hematocrit is increasing and anticipated to exceed 43%. The dose of cytoreductive therapy may be decreased or stopped for safety. However, an increase in cytoreductive therapy dose to control hematocrit, platelets or leukocytes levels is not allowed and participants cannot start new cytoreductive therapy. Clinic visits will be on Weeks 4, 8, 12, 16, 20, 24, 28, and 32.

Participants are considered phlebotomy eligible and should undergo a phlebotomy if **either**

- their confirmed hematocrit is ≥45% and that is at least 3% (absolute) higher than the baseline hematocrit. Confirmation is defined as 2 consecutive hematocrit assessments that are ≥45% and at least 3% higher than the baseline hematocrit.

  or

- a hematocrit ≥48%.

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PART 1b: OPEN-LABEL TREATMENT PHASE (Week 32 through Week 52)

All participants who complete 32 weeks of treatment will be eligible to continue in Part 1b. The duration of dosing in Part 1b is 20 weeks. After a participant and the investigator complete all Week 32 assessments, the participant's treatment assignment is unblinded. All participants will receive rusfertide in Part 1b and will initially be dosed as follows:

- Participants randomized to rusfertide in Part 1a - continue receiving same active dose as at Week 32 unless dose adjustment is required for safety or to maintain hematocrit <45%.
- Participants randomized to placebo in Part 1a - receive 19 mg active dose at Week 32.

Clinic visits will be every 4 weeks (Weeks 36, 40, 44, 48, and 52). The dose should be adjusted to maintain hematocrit <45%. Similar to Part 1a, the dose of cytoreductive therapy may be decreased or stopped for safety (for example, for adverse events), but an increase in dose to control hematocrit, platelets or leukocytes levels is not allowed and participants cannot start new cytoreductive therapy during Part 1b.

PART 2: LONG-TERM EXTENSION PHASE (Week 52 through Week 156)

All participants who complete Part 1b of treatment will be eligible to continue treatment in Part 2. The duration of dosing in Part 2 is 104 weeks. The dose of cytoreductive agents may be adjusted for either safety or efficacy and participants may begin new cytoreductive therapy in Part 2. The first two visits in Part 2 will be 4 weeks apart. Afterwards, clinic visits will be every 12 weeks, with optional visits every 6 weeks if the visits are required for possible dose adjustment.

PART 3: RUSFERTIDE TREATMENT EXTENSION PHASE (End of Part 2 through End of Study)

Participants who complete Part 2 may be eligible for Part 3 if, in the opinion of the investigator, they are continuing to derive benefit from rusfertide and:

- do not have access on the commercial market following local commercial availability under the standard pricing and reimbursement model in a country.

or

- cannot obtain rusfertide through a PTA program.

During Part 3, participants will come to the clinic every 12 weeks. The dose of cytoreductive agents may be adjusted for either safety or efficacy; additionally, participants may begin new cytoreductive therapy in Part 3.

Access to rusfertide following completion of this trial will be determined by local regulatory requirements and available access mechanisms (for example, commercial availability or reimbursement, a PTA program, or other sponsor-determined access mechanism, as applicable).

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EARLY TERMINATION

Participants who discontinue participation before completing Part 2 of the study should undergo the Early Termination assessments and post-treatment safety follow-up. For participants consenting to Protocol Amendment 6 or higher and continuing into Part 3, only safety-related end of study assessments will be collected.

POST-TREATMENT SAFETY FOLLOW-UP

Participants who complete Part 2 at Week 156 without entering Part 3, or who discontinue rusfertide prior to Week 156, will undergo a safety follow-up evaluation approximately 4 weeks after their last dose.

Additionally, participants who permanently discontinue rusfertide at or before Week 156 and do not enter Part 3 will be contacted (for example, by telephone) approximately 6 and 12 months after their last dose to assess the occurrence of any new cancer events.

COVID-19 PANDEMIC AND OTHER DISASTER MANAGEMENT

Disasters such as the COVID-19 pandemic may disrupt normal study operations and require study modifications to maintain participant safety and integrity of the trial. Appendix 4 describes management of study disruption due to COVID-19 and other disasters.

STOPPING RULES

Study Stopping Rules

Sequential boundaries will be used to monitor development of human cancer (Ivanova 2005) in evaluable participants. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at 0.05, assuming the human cancer development rate in this population to be 0.08 (Khanal 2016, Masarova 2016).

If a cancer-development event is observed in the evaluable population, the sponsor (or sponsor's medical monitor/designee) will be informed and will perform an ad hoc medical review in conjunction with the investigator's assessment.

A cancer-development event will contribute toward the observed number of cases for the Pocock-type stopping boundary if it is assessed as possibly related or related to rusfertide by either the investigator or the sponsor.

If the total number of such cases observed in the rusfertide-treated group is equal to or exceeds "x" out of "n" evaluable participants during the study duration, accrual and dosing will be halted pending further sponsor review.

If the study is halted due to safety concerns, or if the study stopping rules as detailed in Section 9.3.1 are triggered, the study can only be restarted after regulatory authority approval via a substantial amendment.

Participant Stopping Rules

Participant participation in the study must stop for any of the following reasons:

- Stage 2 or higher basal cell carcinoma.
- Stage 2 or higher squamous cell carcinoma of the skin.
- New cancer requiring therapy that would interrupt study drug for more than 4 weeks.
- Recurrence of cancer except for local recurrence of inadequately treated non-melanomatous skin cancer. Inadequate treatment includes treatment that is not intended to be curative and treatment that leaves residual tumor.
- Persistent (confirmed at least 8 weeks later) increase in leukocytes (>25x10^9/L with at least a 50% increase in baseline leukocyte count from Day 1 of Week 0) in either Part 1a or Part 1b.
- Persistent (confirmed at least 8 weeks later) increase in platelets (>1500x10^9/L) in either Part 1a or Part 1b.

Participants with persistently elevated leukocytes or platelets in Part 2 or in Part 3 are allowed to remain in the study provided the investigator begins cytoreductive therapy or adjusts concurrent cytoreductive therapy to control the elevated counts.

Number of participants (planned): Randomize approximately 250 participants (125 per treatment group).

Diagnosis and main criteria for inclusion:

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Inclusion Criteria: Participants must meet ALL of the following inclusion criteria:

1. Male and female participants aged 18 (or the minimum country specific age of consent if >18) years or older.
2. Participant understands the study procedures, is willing and able to adhere to study requirements and agrees to participate in the study by giving written informed consent.
3. Meet revised 2016 World Health Organization (WHO) criteria for the diagnosis of polycythemia vera (Appendix 1).
4. Phlebotomy requiring defined as **ALL** of the following:
   a. At least 3 phlebotomies due to inadequate hematocrit control in 28 weeks before randomization or at least 5 phlebotomies due to inadequate hematocrit control in 1 year before randomization, **and**
   b. Last phlebotomy due to inadequate hematocrit control within 3 months before randomization, **and**
   c. No phlebotomy within 6 days prior to randomization (do not include day of phlebotomy and day of randomization in the 6-day count).

   Note: Phlebotomies performed within an 8-day period will be counted as a single phlebotomy.
5. Complete Blood Count (CBC) values immediately prior to randomization:
   a. Hematocrit <45%,
   b. WBC 4000/µL to 20,000/µL (inclusive) and
   c. Platelets 100,000/µL to 1,000,000/µL (inclusive).
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
7. Women of childbearing potential (WOCBP) agree to use medically acceptable contraception (<1% annual failure rate) during the study and for 30 days after the last dose of study drug (Appendix 2).
8. A female participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 30 days after receiving the last dose of study medication.
9. Men with partners of childbearing potential agree to use medically acceptable contraception (<1% annual failure rate) during the study and for 90 days after the last dose of study drug (Appendix 2). In addition, men must use a condom during the study and for 90 days after the last dose of study drug regardless of the partner's childbearing potential.
10. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last dose.
11. Participants receiving cytoreductive therapy at randomization must be on a stable polycythemia vera (PV) therapy regimen as follows:
    a. Hydroxyurea - at least 2 months.
    b. Janus kinase inhibitor - at least 2 months.
    c. Interferon - at least 6 months.

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Note: A "stable dose regimen" of cytoreductive therapy does not mean an unchanged dose regimen. Temporary adjustments in dose regimen or temporary suspension of dosing are allowed. However, the total weekly dose of hydroxyurea and JAK inhibitor or total monthly dose of interferon **may not be higher at randomization than the dose at the beginning of the pre-randomization** observation period. The pre-randomization observation period is 2 months for hydroxyurea and JAK inhibitor and 6 months for interferon.

12. Participants treated with phlebotomy alone at randomization must have stopped:
    a. Hydroxyurea at least 2 months before screening.
    b. JAK inhibitor at least 2 months before screening.
    c. Interferon at least 6 months before screening.

Exclusion Criteria: Participants must not meet ANY of the following exclusion criteria to be enrolled:

1. Clinically meaningful laboratory abnormalities at Screening including, but not limited to:
    a. Estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2.
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 × upper limit of normal (ULN).
    c. Total bilirubin >1.5 × ULN.

    Note: Screening laboratory tests with abnormal results (if considered by the investigator to be transient and inconsistent with the participant's clinical condition) may be repeated within the screening window to confirm abnormal results. If results return to protocol acceptable limits within the screening period, the participant may enter the study. Use local labs for CBC and use central labs for all other eligibility lab tests.
2. Participants who require phlebotomy at hematocrit levels lower than 45%.
3. Pregnant or lactating females.
4. Clinically significant thrombosis (for example, deep vein thrombosis or splenic vein thrombosis) within 2 months prior to randomization.
5. Active or chronic bleeding within 2 months prior to randomization.
6. Meets the criteria for post-polycythemia vera myelofibrosis as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).
7. Any infection requiring systemic therapy within 1 month of dosing except controlled HIV, hepatitis B, and hepatitis C. Prophylactic therapies are allowed.
8. Any serious or unstable medical condition (for example, poorly controlled HIV infection) or uncontrolled psychiatric condition as judged by the investigator that would impair the participant's ability to participate in the study.
9. Major surgical procedure within 2 months prior to randomization unless the participant has fully recovered from surgery or planned major elective surgery during the study.
10. History of invasive malignancies within the last 5 years, except
    a. localized cured cancer (for example, prostate cancer and cervical cancer)

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b. localized cured in situ or stage 1 squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or in situ melanoma of the skin.

11. Participants with 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 the required dermatology examination at screening unless the cancer is adequately treated (that is treatment that is expected to be curative, such as Mohs surgery) before randomization. Note: Suspicious lesions should be biopsied and results available before randomization.
12. Participants with active alcohol or drug addiction that would interfere with their ability to comply with study requirements.
13. Participants who do not complete at least 4 days of Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) assessments within 1 week prior to randomization.
14. Receipt of an investigational agent within 2 months or 5 half-lives, whichever is longer, prior to randomization.
15. Received busulfan, pipobroman or ^{32}Phosphorus within 7 months prior to screening.
16. Participants with hypersensitivity to rusfertide or to any of the excipients or placebo.
17. Participants with any lesion or mass detected by physical examination or imaging during screening that is suspicious for malignancy unless evaluated and assessed to be not malignant.

Investigational product, dose and mode of administration:

Rusfertide will be provided in a convenience kit containing the drug as a lyophilized powder in a glass vial with an accompanying vial or syringe of diluent for reconstitution.

The following dose strengths are provided: 9.5 mg, 19 mg, 28 mg, 41 mg, and 54 mg rusfertide. The maximum daily dose is 82 mg. The maximum total weekly dose of rusfertide in Parts 1a and 1b is 82 mg and the maximum total weekly dose in Part 2 and Part 3 is 108 mg.

Study drug will be administered by SC injections.

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Reference therapy, dose, and mode of administration: Placebo

Placebo will be provided as a lyophilized powder in a glass vial with an accompanying vial or syringe of diluent for reconstitution. Placebo dose strengths and administration are identical to those of rusfertide.

Duration of treatment: Individual participants will participate in this study as follows:

- Screening: up to 6 weeks.
- Part 1a - Double-blind: 32 weeks (Week 0 to Week 32).
- Part 1b - Open-label: 20 weeks (Week 32 to Week 52).
- Part 2 - Long-term extension: 104 weeks (Week 52 to Week 156).
- Post-treatment safety follow-up: 4 weeks after last dose of study drug for participants who do not continue into Part 3.

- Part 3 - Rusfertide treatment extension: End of Part 2 (Week 156) to End of Study.

Study endpoints:

Primary endpoint:

Proportion of participants achieving a response starting at Week 20 through Week 32 (inclusive) who receive rusfertide compared to placebo. A response is defined as absence of phlebotomy eligibility. Phlebotomy eligibility is defined as **either**:

- a confirmed hematocrit ≥45% and that is at least 3% higher than the baseline hematocrit.

  Confirmation is defined as 2 consecutive hematocrit assessments that are ≥45% and at least 3% higher than the baseline hematocrit

  or

- a hematocrit ≥48%.

Hematocrit values from each clinical site's local laboratory will be used for the primary endpoint.

Key secondary endpoints: Comparison of rusfertide to placebo

1. Mean number of phlebotomies between Weeks 0 through 32 (inclusive).
2. Proportion of participants with all hematocrit values <45% between Week 0 through Week 32 (inclusive). A single hematocrit value ≥45% is allowed. Hematocrit values from each clinical site's local laboratory will be used for this endpoint.
3. Mean change from baseline at end of Part 1a (Week 32) in the Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a total T-score.
4. Mean change from baseline at end of Part 1a (Week 32) in the Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF) Total Symptom Score (TSS7). The weekly TSS7 at Week 32 will be calculated by averaging daily TSS7 over a 7-day interval leading to Week 32 (inclusive).

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Other secondary endpoints:

Part 1a - Week 0 through Week 32 (inclusive):

Comparison of rusfertide to placebo during randomized, double-blind, placebo-controlled, add-on parallel phase

PV-focused PRO-related secondary endpoints in participants with moderate or severe symptoms:

- Mean change from baseline at end of Part 1a (Week 32) in the PROMIS Fatigue Short Form 8a total T-score among participants who have moderate or severe symptoms at baseline.
- Mean change from baseline at end of Part 1a (Week 32) in the Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF) Total Symptom Score-4 items (TSS4) among participants who have moderate or severe symptoms at baseline. TSS4 is the sum of 4 items of the MFSAF (fatigue, itching, night sweats, and abdominal discomfort). The weekly TSS4

at Week 32 will be calculated by averaging daily TSS4 over a 7-day interval leading to Week 32 (inclusive).

- Mean change from baseline at end of Part 1a (Week 32) in the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Problems with Concentration among participants who have moderate or severe symptoms at baseline.
- Proportion of participants with a meaningful within-person change at Week 32 in the PROMIS Fatigue SF 8a T-score, MFSAF TSS4, and MPN-SAF problems with concentration among participants who have moderate or severe symptoms at baseline.

Other PRO-related secondary endpoints:

- Mean change from baseline at each scheduled assessment in individual questions and the total fatigue T-score based on PROMIS® Short Form 8a.
- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MFSAF v4.0.
- Proportion of participants with a meaningful within-person change at Week 32 in the PROMIS Fatigue SF 8a total T-score, MFSAF TSS4, and MPN-SAF problems with concentration.
- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MPN-SAF TSS 10.
- Mean change from baseline in Patient Global Impression of Severity (PGI-S) at each scheduled assessment.
- Proportion of participants with at least one unit improvement in the PGI-S from baseline, that is a ≥ 1 point decrease in the PGI-S, for example, a change from "Moderate (2)" to "Mild (1)" or "Mild (1)" to "None (0)" at each scheduled visit.
- Proportion of participants with a rating on the PGI-C of either "much better" or "a little better" at each scheduled assessment.
- Mean PGI-C at each scheduled assessment.
- Mean change from baseline in the individual domain scores and the total EORTC QLQ-C30 score at Week 32.

Hematocrit and Phlebotomy-related secondary endpoints:

- Median time to first hematocrit ≥45% after randomization.
- Proportion of participants with at least one hematocrit ≥48%.
- Proportion of participants who maintain absence of phlebotomy eligibility.

Parts 1a + 1b: Week 0 through Week 52:

- Proportion of participants originally randomized to rusfertide achieving absence of phlebotomy eligibility (durable response) for 52 weeks.
- Median time to first confirmed hematocrit ≥45% during Part 1b excluding Part 1a.

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- Median time to first phlebotomy during Part 1b excluding Part 1a.

Safety:

Part 1a + Part 1b + Part 2 + Part 3: Week 0 through End of Study:

- Frequency distribution will be presented for treatment emergent adverse events (TEAEs), serious TEAEs and AEs of special interest (AESI).
- Clinical safety laboratory tests, physical examination, vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate) and 12-lead electrocardiogram (ECG) findings will be summarized as applicable.

Concomitant medications and therapies:

Permitted:

Participants should receive appropriate care for PV. Antiplatelet agents (for example, low-dose aspirin and clopidogrel) and anticoagulants (for example, vitamin K antagonists and novel oral anticoagulants) are permitted. Participants should receive full supportive care for any other underlying conditions.

- Multivitamins are allowed if they have a normal recommended daily dose of iron (for example, ≤ 20 mg/day).
- Cytoreductive therapy (for example, hydroxyurea, interferon, ruxolitinib and other approved JAK inhibitors) is allowed if the participant was receiving the cytoreductive agent at the time of screening.
  - In Part 1a and Part 1b, the dose of cytoreductive therapy may be decreased or stopped for safety but cannot be increased above the Week 0 dose for efficacy (for example, to control hematocrit, platelets, or leukocytes levels) and participants cannot start new cytoreductive therapy.
  - In Part 2 and Part 3, the dose of cytoreductive therapy may be changed for safety or to control hematocrit, platelets, or leukocytes levels. Participants may also start new cytoreductive therapy.

Prohibited:

- PV-specific therapies other than phlebotomy, hydroxyurea, interferon, ruxolitinib, and other JAK inhibitors are prohibited.
- Investigational agents must be discontinued within 2 months or 5 half-lives prior to randomization and are not allowed during the study.
- Iron supplementation at doses above 20 mg/day is not allowed.

Statistical methods:

Power and Sample Size:

Approximately 250 participants will be randomized to rusfertide and placebo in a 1:1 ratio (125 participants per treatment group).

Assuming a response rate (absence of phlebotomy-eligibility) during Weeks 20 to 32 (inclusive) of approximately 25% on placebo and 50% from rusfertide, 95 participants will be required per

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treatment group to detect a difference in the proportion of participants treated with rusfertide achieving clinical response compared to participants treated with placebo at a 0.05 level of significance (2-sided) with approximately 95% power using a z-test based on large sample approximation to binomial distribution.

To detect a treatment difference between rusfertide and the placebo groups in the mean number of phlebotomies in Part 1a and the proportion of participants with all hematocrit values <45% (a single transient hematocrit value ≥45% is allowed) during Part 1a, a sample size of 106 participants will be required per treatment group with at least 95% power.

To detect a treatment difference in mean change from baseline in the total score based on PROMIS and the total score based on MFSAF, a sample size of 125 participants per treatment arm will have approximately 80% power using a two-sample t-test with a 0.05 two-sided level of significance.

Analysis Sets:

- Intent to Treat (ITT): All randomized participants according to the treatment assigned at randomization.
- Full Analysis Set (FAS): All randomized participants according to the treatment assigned at randomization (ITT principle) and have a baseline and at least one postbaseline assessment in Part 1a.
- Safety Analysis Set (SAS): All randomized participants who receive at least one dose of study drug. Participants will be analyzed according to the study treatment they actually receive.
- Per Protocol Set (PPS): Subset of participants in ITT who have received at least one dose of study drug with no major protocol deviations at study entry or during the study. Participants will be analyzed according to the study treatment they actually receive.
- Pharmacokinetic/Pharmacodynamic Analysis Set (PKPDAS): Subset of participants in ITT who have received at least one dose of study drug and have at least one baseline and one post baseline PK/PD measurement.

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General:

Baseline is defined as the last assessment done on the date prior to or the same date of the first dose of study drug, unless otherwise specified. For MFSAF v4.0, the baseline will be the average score of the 7-day interval immediately on or prior to first dose date. The weekly total symptom score at each scheduled visit will be calculated by averaging daily total symptom scores over a 7-day interval during the week leading to the scheduled visit (inclusive). The individual domain scores and the total score obtained during screening will be used as baseline value for the EORTC QLQ-C30.

All analyses and summary statistics will be presented by treatment arm for Part 1a. Combined analyses of the 3 parts will focus on the maintenance and durability of effect of rusfertide as well as impact of participants being treated with rusfertide after 32 weeks on treatment with placebo.

Descriptive statistics, including the numbers and percentages for categorical variables and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided by treatment arm.

Efficacy Analyses:

Efficacy data for Parts 1a, 1b and 2 will be analyzed separately as well as for the whole duration of treatment to assess maintenance of effect and safety. Descriptive statistics will be used to evaluate differences in demographic and baseline characteristics.

For the primary analysis, proportions of participants with clinical response starting at Week 20 through Week 32 (inclusive) will be compared between rusfertide and placebo using Cochran-Mantel-Haenszel (CMH) 2-sided test at a 0.05 level of significance, with adjustment for stratification factor of ongoing PV therapies (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other). Clinical response is defined as absence of phlebotomy eligibility. Phlebotomy eligibility is defined as **either** a confirmed hematocrit ≥45% and that is at least 3% (absolute) higher than the baseline hematocrit; **or** a hematocrit ≥48. Confirmation is defined as 2 consecutive hematocrit assessments that are ≥45% and at least 3% higher than the baseline hematocrit.

In addition to the primary comparison, key secondary endpoints, (1) mean number of phlebotomies starting at Week 0 through Week 32 (inclusive), (2) proportion of participants with all hematocrit values <45% between Week 0 through Week 32 (inclusive) (a single hematocrit value ≥45% is allowed), (3) mean change from baseline in PROMIS Fatigue SF 8a total fatigue T-score at Week 32, and (4) mean change from baseline in MFSAF TSS7 at Week 32 will be tested for treatment differences through closed testing procedure in a single hierarchical order.

If the primary endpoint is statistically significant at a 0.05 level of significance (2-sided), the mean number of phlebotomies (1st key secondary) will be tested at a 0.05 level of significance (2-sided). If the 1st key secondary endpoint is significant then the proportion of participants with all hematocrit values <45% (a single hematocrit value ≥45% is allowed), between Week 0 through Week 32 (inclusive) will be compared between rusfertide and placebo using CMH at a 0.05 level of significance (2-sided) with adjustment for stratification factor. If the 2nd key secondary endpoint is significant then the 3rd key secondary endpoint of treatment difference between rusfertide and placebo will be analyzed for mean change from baseline in PROMIS Fatigue SF 8a total fatigue T-score at Week 32 at 0.05 level of significance (2-sided). If the 3rd key secondary is significant at a 0.05 level of significance (2-sided) then the 4th key secondary endpoint of treatment difference between rusfertide and placebo will be analyzed for mean change from baseline in total MFSAF TSS7 at Week 32 at 0.05 level of significance (2-sided).

The 3 PV-focused PRO-related secondary endpoints in participants with moderate or severe symptoms at baseline will be compared for treatment differences using ITT population. To determine the cut-offs for "moderate"/"severe," the distribution of the outcome measure score was categorized at baseline using the PGI-S. Using this approach, moderate or severe symptoms for PROMIS Fatigue SF 8a T-score are defined as baseline PROMIS Fatigue SF 8a total T-score ≥58.8; for MFSAF TSS4 are defined as baseline MFSAF TSS4 ≥9.1. For problems with concentration, moderate or severe symptoms are defined as a baseline MPN-SAF problems with concentration ≥ 4 (Emanuel 2012).

In general, all categorical efficacy endpoints will be analyzed using CMH test at a 0.05 level of significance (2-sided), with adjustment for stratification factor of type of ongoing PV therapy. All continuous endpoints will be analyzed using either an Analysis of Covariance (ANCOVA) model with two factor main effects of treatment and stratification and baseline value as a covariate or a mixed model for repeated measures (MMRM) model and will include treatment and stratification as fixed factors and baseline score as a covariate. The MMRM model will use an unstructured within participant covariance matrix and a restricted maximum likelihood (ReML) estimation method.

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To estimate the time to events such as first phlebotomy or first hematocrit ≥ 45% Kaplan-Meier estimates will be presented by treatment group adjusted for stratification.

No multiplicity adjustments will be made for other secondary endpoints.

The main goal of Part 1b and Part 2 is to evaluate maintenance of effect and safety during the extended period of treatment until Week 156. The durability of effect of rusfertide will be evaluated using the proportion of participants who maintain clinical response, defined as absence of phlebotomy eligibility at the end of Part 1b. The point estimate and the confidence interval associated with the estimate will be provided. Additionally, for other endpoints where appropriate, point estimate and the confidence interval associated with the estimate will be provided.

The main goal of Part 3 is to provide access to rusfertide for participants who have completed Part 2 and, in the opinion of the investigator, are continuing to derive benefit from rusfertide therapy. Safety and efficacy data from Part 3 will be summarized as appropriate using descriptive statistics.

Pharmacokinetics (PK):

Individual rusfertide concentration data will be listed and summarized with descriptive statistics (number, arithmetic mean, standard deviation, median, minimum, maximum and geometric mean). Individual and mean rusfertide concentration-time profiles will also be presented graphically.

Serum samples will be evaluated for the presence of antidrug antibodies (ADA) through use of an immunoassay. If ADA is detected in clinical samples, the effect of ADA on PK, safety and efficacy will be explored.

Pharmacodynamics (PD):

PD will be listed for each individual and summarized by frequency counts for discrete categories. Individual data will be listed for each individual and summarized by nominal sampling time point and treatment group with descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). A summary of change-from-baseline at each protocol specified time-point by treatment group will also be presented.

Safety and Tolerability:

Quantitative safety data will be summarized using descriptive statistics and frequency distributions. Qualitative safety data will be summarized by frequencies and percentages. All summaries will be presented by treatment arms. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Concomitant medications will be coded using World Health Organization (WHO) drug dictionary.

Laboratory evaluations, vital signs assessments and ECG parameters will be summarized by treatment group and protocol specified collection time point. A summary of change-from-baseline at each protocol specified time-point by treatment group will also be presented.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BAT	Best available therapy
BLOCF	Baseline observation carried forward
BSH	British Society for Haematology
BUN	Blood urea nitrogen
CAS	Completers Analysis Set
CBC	Complete blood count
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum concentration
C_{trough}	Concentration of study drug immediately before the next dose of study drug is administered
CMH	Cochran-Mantel-Haenszel
COA	Clinical outcome assessment
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events

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Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EHA	European Haematology Association
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOS	End of study
EOT	End of treatment
EPAR	European public assessment report
EPO	Erythropoietin
ESMO	European Society of Medical Oncology
ET	Early termination
EU	European Union
FAS	Full Analysis Set
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBc	Hepatitis B core antibody
HBsAG	Hepatitis B surface antigen
HCAb	Hepatitis C antibody
HCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

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Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
IL-6	Interleukin 6
IND	Investigational New Drug Application
INR	International reference range
IRB	Institutional Review Board
ISR	Injection site reactions
ITT	Intent to Treat
IUS	Intrauterine hormone-releasing system
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
IxRS	Interactive voice randomization (IVR) or Interactive Web Response (IWR) System
JAK2	Janus kinase 2
LAM	Lactational amenorrhea method
LOCF	Last observation carried forward
LPF	Lyophilized Drug Formulation
LTE	Long term extension
MAR	Missing at random
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin content
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MFSAF v4.0	Myelofibrosis Symptom Assessment Form version 4.0
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
MPN	Myeloproliferative neoplasm
MPN-BP	Blast-phase myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

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Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
NCS	Not clinically significant
NCT	National Clinical Trial
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PAP	Psychometric Analysis Plan
PD	Pharmacodynamic
PFS	Patient Global Impression of Change
PGI-C	Progression free survival
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic
PKPDAS	Pharmacokinetic/Pharmacodynamic Analysis Set
PPS	Per Protocol Set
PR interval	On ECG tracing: interval from start of P wave to start of the R wave
PRO	Patient reported outcome
PROMIS®	Patient-Reported Outcomes Measurement Information System
PT	Prothrombin time
PTA	Post-trial access
PTT	Partial thromboplastin time
PV	Polycythemia vera
QoL	Quality of Life
QRS duration	On ECG tracing: duration from the start of the Q wave to the end of the S wave
QT interval	On ECG tracing: interval from the start of the Q wave to the end of the T wave
QTcF interval	QT interval corrected for heart rate according to Fridericia's formula
rasH2	c-Ha-ras oncogene
RBC	Red blood cell
RCM	Red cell mass
RDW	Red cell distribution width
ReML	Restricted maximum likelihood

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Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
RR interval	On ECG tracing: the time elapsed between two successive R-waves of the QRS signal
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SC	Subcutaneous; Subcutaneously
SUSAR	Suspected unexpected serious adverse reaction
TSAT	Transferrin saturation
TSS4	Total Symptom Score-4 items
TSS7	Total Symptom Score-7 items
TSS 10	Total Symptom Score 10
ULN	Upper limit of normal
US	United States, Ultrasound
V617F	Valine-to-phenylalanine substitution at position 617
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of childbearing potential

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5. INTRODUCTION

Takeda Development Center Americas, Inc. (Takeda) is developing rusfertide (also known as PTG-300 or TAK-121), an injectable peptide mimetic of the endogenous hormone hepcidin, as a potential treatment for polycythemia vera (PV).

5.1. Overview of Polycythemia Vera and Current Treatment Options

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) in which there is an overproduction of red blood cells (RBCs). PV occurs in all populations, and all ages. The median age at diagnosis is approximately 60 years. Approximately one-quarter of cases present before age 50 years and one-tenth before age 40 years. The main underlying cause of PV, identifiable in 95% of adult patients, is a mutation in the JAK2 gene with a valine-to-phenylalanine substitution at position 617 (V617F) (Baxter 2005, Levine 2005). This myeloproliferative neoplasm is characterized by elevated numbers of red blood cells, diversely associated with thrombocytosis, leukocytosis and splenomegaly (James 2005). Erythrocytosis is linked to an increase in blood viscosity. Symptoms of hyperviscosity include chest and abdominal pain, myalgia and weakness, fatigue, headache, blurred vision, paresthesia, and slow mentation (Keohane 2013). These symptoms, particularly fatigue and cognitive impairment, are exacerbated by treatment that often results in severe iron deficiency.

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Hyperviscosity of the blood increases the risk of thrombosis, both arterial and venous, and treatment is largely designed to reduce thrombotic risk by lowering a patient's hematocrit. Possible complications of PV include venous and arterial thrombosis, splenomegaly, peptic ulcers, gout, and pruritus. PV is associated with shortened survival, with a median survival of approximately 14 years in patients over the age of 60 (Tefferi 2019). PV can transform to secondary myelofibrosis (that is, post-PV myelofibrosis) or secondary acute myeloid leukemia, also termed blast-phase MPN (MPN-BP).

The most important therapeutic goal for treating adult patients with PV is maintaining hematocrit below 45% (McMullin 2019, Tefferi 2019) and thereby reducing thrombotic events. A prospective, randomized trial compared maintaining hematocrit <45% with maintaining hematocrit between 45% and 50% (Marchioli 2011, Marchioli 2013). Maintaining hematocrit <45% decreased the risk of thrombotic events and cardiovascular death significantly. Maintaining hematocrit <45% is recommended by European Haematology Association guidelines (Vannucchi 2011), European Society for Medical Oncology guidelines (Vannucchi 2015), British Society of Haematology guidelines (McMullin 2019) and National Comprehensive Cancer Network guidelines (Mesa 2017).

A key element in treating a PV patient is to identify the potential risk to develop major thrombotic complications. For treatment initiation, patients are categorized into two risk categories: high-risk (age ≥60 years or thrombosis history) and low-risk (absence of both risk factors). Therapeutic phlebotomy is the mainstay of treatment of patients with PV, in combination with once-or twice daily low-dose aspirin (Tefferi 2019) and is the initial therapy recommended for low-risk PV patients. More importantly, intermittent phlebotomy results in

fluctuations in the hematocrit level, when it has been shown that continuously maintaining the hematocrit below 45% was associated with lower risk of thrombosis. Cytoreductive therapy is recommended for high-risk PV patients as well as those low-risk patients with poor tolerance of phlebotomy, frequent phlebotomy requirement, symptomatic or progressive splenomegaly, severe disease-related symptoms, progressive thrombocytosis, or progressive leukocytosis. The first line cytoreductive therapy for patients of any age is hydroxyurea (also known as hydroxycarbamide). Interferon-α-2a or ropeginterferon alfa-2b should be considered as second-line therapy in younger patients, and busulphan should be considered as second-line therapy in patients aged >70 years old. Ruxolitinib is recommended only after treatment failure with hydroxyurea, interferon and busulphan (Tefferi 2019).

Patients with PV often present with iron deficiency (Ginzburg 2018). Iron deficiency is exacerbated by the iron-depleting effects of therapeutic phlebotomies that in part reduce erythrocytosis by limiting the availability of iron. The deleterious effects of iron deficiency include fatigue, cognitive impairment, reduced physical performance, itching, and pica. The beneficial effects of cytoreductive agents in reducing symptoms in PV patients may be due, in part, to reducing iron deficiency by decreasing the number of phlebotomies required to maintain hematocrit levels below 45% (Verstovsek 2017).

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5.2. Overview of Rusfertide

Hepcidin is a peptide hormone that is the body's main regulator of iron homeostasis (Liu 2016, Ruchala 2014). Hepcidin regulates iron stores by binding to ferroportin and thereby blocking iron export from enterocytes and from macrophages. The inhibition of iron export from macrophages causes an iron-restricted anemia even in the setting of normal or elevated total body iron stores. Elevated hepcidin levels appear to mediate anemia of inflammation, also called anemia of chronic disease (Ganz 2019).

Rusfertide is a peptidic agent structurally related to natural hepcidin that mimics its inhibitory activity on ferroportin. In wild type mice, rats and cynomolgus monkeys a single SC or intravenous injection of rusfertide caused a transient decrease in serum iron levels. Chronic rusfertide dosing in rats and cynomolgus monkeys caused a dose-related anemia that is thought to be due to restricted iron availability for erythropoiesis. Rusfertide has not been tested in pre-clinical models of PV. However, a minihepcidin was shown to be effective for reducing hematocrit and splenomegaly in a mouse model of PV (Casu 2016).

For further details of the rusfertide clinical program, consult the rusfertide IB.

5.2.1. Nonclinical Studies

Principal findings in nonclinical toxicology studies are alterations in red cell mass. Rusfertide has no apparent effect on cardiovascular, respiratory, or neurobehavior systems. Rusfertide is not genotoxic. Rusfertide may affect embryo-fetal development.

Studies in healthy cynomolgus monkeys provide support for testing rusfertide for the treatment of PV. In these studies, rusfertide had effects that were consistent with its proposed mechanism

of action as a hepcidin mimetic. In a 39-week toxicology study in non-human primates, the once weekly SC injection of rusfertide at 0.6, 2 and 6 mg/kg/dose was clinically well tolerated by the monkeys at doses up to 2 mg/kg/dose. At a dose of 6 mg/kg/dose, one Main male monkey died from complications secondary to pharmacologically driven, long-standing anemia. (Hemoglobin was 23 g/L on Day 182 [last test before it was found dead], compared to 135 g/L on Day -7 [predose]).

There were no rusfertide-related changes in clinical signs, body weights or body weight gains, ophthalmology, blood pressure, electrocardiography, coagulation, clinical chemistry, urinalysis, and organ weights at any dose level tested.

Rusfertide at ≥ 0.6 mg/kg/dose resulted in reductions in RBC parameters (red blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin, and/or mean corpuscular hemoglobin concentration), which represented the pharmacology mediated anemia, and subsequent regenerative processes (increases in platelets, absolute/relative reticulocyte counts, and red cell distribution width at ≥2 mg/kg/dose).

At the end of the recovery period, all rusfertide related findings observed during the treatment period reversed completely with the exception of the persistent elevations in platelet counts and red cell distribution width at 6 mg/kg/dose, as well as SC fibrosis at the dosing site at ≥0.6 mg/kg/dose and intracellular pigment (hemosiderin) in the spleen and liver at 6 mg/kg/dose. However, these changes were to a lesser extent than during the treatment period, indicating an incomplete, but progressive ongoing reversal.

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Rusfertide was also evaluated for embryo-fetal development toxicity in rats and rabbits and fertility and early embryonic development toxicity in both male and female rats. The maternal no-observed-adverse-effect level (NOAEL) was 3 mg/kg/dose and the NOAEL for the embryo-fetal development was 0.3 mg/kg/dose in the definitive embryo-fetal development toxicity study in rats. The maternal NOAEL was 1 mg/kg/dose and the NOAEL for the embryo-fetal development was 0.3 mg/kg/dose in the definitive embryo-fetal development toxicity study in rabbits. The NOAEL for paternal toxicity and the NOEL for effects on male fertility and early embryonic development were considered to be 10 mg/kg/dose in fertility and early embryonic development toxicity study in male rats. The NOAEL for maternal toxicity and the NOEL for effects on female fertility and early embryonic development were 3 mg/kg/dose in fertility and early embryonic development toxicity study in female rats. The embryo-fetal development toxicity studies in rats and rabbits suggest that rusfertide has the potential to affect fetal development in humans.

A Good Laboratory Practice definitive 26-week carcinogenicity study in transgenic rasH2 mice was conducted. The rasH2 model was developed as an alternative to the lifetime mouse bioassay to predict the carcinogenic potential of chemicals. This model suggests that rusfertide may have carcinogenic potential. No rusfertide-related mortality was noted. Macroscopic findings of masses in skin/subcutis in several males administered ≥6.25 mg/kg/dose and females administered ≥12.5 mg/kg/dose frequently correlated microscopically with rusfertide-related benign squamous papilloma and/or malignant squamous cell carcinoma in the skin/subcutis;

these macroscopic observations were made in multiple skin/subcutis locations on the body, and close proximity to a SC injection site was limited to one instance. No other rusfertide-related macroscopic observations were noted. Rusfertide-related effects on the incidences or types of neoplasms were noted in skin/subcutis (benign papilloma and malignant squamous cell carcinoma) from males administered ≥6.25 mg/kg/dose and females administered ≥12.5 mg/kg/dose (exposure ratio at 6.25 mg/kg/dose is approximately 5x margins over the human exposures at the highest dose of 108 mg rusfertide in a 60 kg human). No evidence of metastasis from these skin/subcutis neoplasms was noted microscopically for animals administered rusfertide at any dose level. Consult the rusfertide IB for further details.

5.2.2. Clinical Studies

To date, more than 380 participants have been enrolled in the rusfertide clinical program. Rusfertide has been studied in multiple Phase 1 studies in healthy participants. Two Phase 2 studies in participants with PV (REVIVE [PTG-300-04] and PACIFIC [PTG-300-08]) have been completed. The Phase 3 study VERIFY (PTG-300-11) and the long-term extension study THRIVE (PTG-300-21) are ongoing. Takeda has also completed two Phase 2 studies of rusfertide in participants with β-thalassemia (PTG-300-02 and PTG-300-03) and a Phase 2 study in participants with hereditary hemochromatosis (PTG-300-06).

Two formulations have been used in clinical trials conducted in participants with PV. In the Phase 2 trials (PTG-300-04 and PTG-300-08), rusfertide was formulated as a liquid formulation dispensed into a 1 mL PFS at 0.5 mL or 1.0 mL fill volume for SC administration. For the Phase 3 trial (PTG-300-11), an LPF was developed for improved product stability and was supplied in a glass vial with an accompanying diluent for reconstitution. The LPF was also used in the long-term extension trial (PTG-300-21), which enrolled participants who completed the Phase 2 trial PTG-300-04.

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For the most current clinical trial data, consult the rusfertide IB.

5.2.2.1. Clinical Pharmacology of Rusfertide

The first Phase 1 study was a randomized, double blind, placebo controlled, first-in-human, single ascending dose and repeat dose study of rusfertide administered SC as an aqueous liquid formulation in 62 healthy male participants to evaluate safety/tolerability, PK and PD activity (as assessed by the effect on serum iron parameters). Participants received single doses of 1 mg to 80 mg rusfertide or two 40 mg doses 1 week apart.

Following single dose administration of rusfertide there was a dose-related reduction in serum iron with a maximal reduction of approximately 65% from baseline. The relationship between dose and effect appeared to plateau at 20 mg with higher doses resulting in a longer duration of effect. This effect was sustained for at least 72 hours at higher doses. In participants that received two 40 mg doses 1 week apart (QW×2) the effects on iron were comparable for both 40 mg doses. Serum iron levels did not return to baseline prior to the second dose. Serum iron levels generally returned to baseline approximately 1 to 2 weeks following the second dose of

rusfertide. Following single dose administration AUC and C_{max} increased with dose; however, the increase was less than dose-proportional over the range of 1 mg to 80 mg.

In the ongoing Phase 2 study in polycythemia vera, rusfertide plasma concentrations in participants receiving hydroxyurea in addition to phlebotomy and participants receiving interferon in addition to phlebotomy were comparable to those receiving phlebotomy alone.

5.2.2.2. Rusfertide Clinical Safety

Overall, rusfertide has been well tolerated by participants. The most common TEAEs were ISRs and anemia. Increases from baseline platelet counts have been observed after initial rusfertide exposure. Mean platelet counts stabilized after continued rusfertide administration. Although some participants experienced sustained increases in platelet counts above 1000×10^9/L for at least 8 weeks, these episodes were not generally associated with clinically significant bleeding events. Other TEAEs experienced by participants are typical of those expected for participants with the underlying conditions and for the general population and include fatigue, pruritus, headache and arthralgia.

Patients with PV have an increased risk of developing other cancers (Fallah et al. 2011), especially skin cancers (Pemmaraju et al. 2023). The inherent risk associated with PV is further exacerbated by treatment with hydroxyurea or JAK inhibitors (Barbui et al. 2019; Lin et al. 2022) and by having a history of prior cancer (Wang et al. 2025). Cancer events were reported in participants' medical history and diagnosed during both screening and while taking part in rusfertide clinical trials. Patients with PV are also at risk for developing post-PV myelofibrosis as well as leukemia (Masarova 2016).

For further details of the rusfertide clinical program, consult the rusfertide IB.

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5.2.2.3. Rusfertide Clinical Efficacy in PV Participants (Phase 2 Protocol PTG-300-04)

Takeda conducted a Phase 2 trial (PTG-300-04) that included both high-risk and low-risk PV participants. This study uses a dose escalation design with participants receiving rusfertide doses ranging from 10 mg to 120 mg administered subcutaneously as the Phase 2 liquid formulation. Based on the clinical response participants received rusfertide generally once a week, and less frequently twice a week, or once every 2 weeks. Rusfertide was added on to each participant's pre-enrollment treatment(s) for PV. Sixty-three participants have been enrolled. A total of 44.4% of participants were low-risk PV; the mean age was 56.4 years (range 27-76); 52.4% of participants underwent 4-5 phlebotomies over 28 weeks before dosing with rusfertide (overall range was 2-9); and the median time between phlebotomies was approximately 43 days. Prior to enrollment, 47.6% received phlebotomy alone, 28.6% received phlebotomy with concurrent hydroxyurea, 15.9% received phlebotomy with concurrent interferon, 4.8% received phlebotomy with concurrent ruxolitinib and 3.2% received phlebotomy with other concurrent therapy (for example, hydroxyurea + ruxolitinib or ruxolitinib + interferon).

Treatment with rusfertide resulted in decreased numbers of erythrocytes and appears effective for maintaining hematocrit <45%. Compared to historical experience in the 28 weeks before

treatment with rusfertide, preliminary data indicates that on-study treatment with rusfertide significantly reduced the rate of phlebotomies ($p < 0.0001$). Twenty-eight participants have completed 28 weeks of dosing. Twenty participants were phlebotomy-free for 28 weeks. Among the 8 participants who required a phlebotomy during the first 28 weeks, 7 were phlebotomy-free after Week 12 when their rusfertide doses stabilized.

5.2.2.4. Rusfertide Clinical Efficacy in PV Participants (Phase 2 Protocol PTG-300-08)

This protocol tested the safety and efficacy of rusfertide for reducing elevated hematocrit levels (>48%) and then maintaining hematocrit <45%. Participants with high-risk or low-risk PV are eligible and concurrent cytoreductive therapy is allowed. Initial treatment is a high dose of rusfertide (as the Phase 2 liquid formulation) at 40 mg administered two times a week (for example, 40 mg Day 1 and 40 mg Day 4 or 5). After a participant's hematocrit is <45% the treatment is changed to 40 mg administered once a week and subsequently the dose is adjusted to maintain hematocrit <45%. Data are available for the first 13 participants, and all 13 participants had rapid decreases in hematocrit to below 45% without the use of phlebotomy. Hematocrit levels remained well controlled after falling below 45% as investigators reduced rusfertide dose to the maintenance regimen.

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5.2.3. Study Rationale

Clinical guidelines for treating PV emphasize the importance of maintaining hematocrit <45% to reduce the risk of thrombotic events and death (National Comprehensive Cancer Network [NCCN]) (Mesa 2017), European Haematology Association (EHA) guidelines (Vannucchi 2011), European Society of Medical Oncology (ESMO) guidelines (Vannucchi 2015), and British Society for Haematology (BSH) guidelines (McMullin 2019). Many PV patients are treated with phlebotomy and/or cytoreductive agents (hydroxyurea, interferon, ruxolitinib) to control hematocrit levels. However, hydroxyurea fails to control hematocrit in approximately 25% of patients and approximately 40% of patients are intolerant or resistant to hydroxyurea. Patients who undergo 3 or more phlebotomies per year while receiving hydroxyurea are at increased risk of adverse outcomes (Alvarez-Larran 2017). Ropeginterferon alfa-2b achieves hematocrit control in 43% to 75% of patients (Besremi [ropeginterferon alfa-2b] European public assessment report [EPAR]) and control develops slowly over many months to years (Gisslinger 2020, Besremi [ropeginterferon alfa-2b] EPAR). Second/third-line therapy with ruxolitinib fails to achieve hematocrit control in 40% of participants (Vannucchi 2015). In an observational study of 2510 PV patients (Grunwald 2020) 94.5% of patients were receiving active treatment at the time of study enrollment but almost half of patients (47.7%) had hematocrit values >45% at study enrollment.

Rusfertide is a peptidic mimetic of hepcidin, the body's master regulator of iron metabolism. The ongoing trial of rusfertide in patients with high-risk and low-risk PV who have high phlebotomy requirements suggest that rusfertide is effective for maintaining hematocrit <45% and for reducing the need for therapeutic phlebotomy. As reported in the Myeloproliferative Neoplasm

Symptom Assessment Form (MPN-SAF), symptom burden, notably fatigue, itching and cognitive impairment improved during treatment with rusfertide.

Although current treatments for PV are effective for many patients, there is a clear need for additional treatments that are effective for maintaining hematocrit continuously below 45% and thereby reduce the risk of thrombotic events. This Phase 3 trial is designed to compare the efficacy of rusfertide to placebo when added on to a participant's ongoing therapy for PV. The primary and key secondary efficacy endpoints represent clinically meaningful benefit to patients: maintenance of hematocrit <45%, which is expected to reduce the risk of thrombotic events, and reduction in the need for phlebotomy.

The study will be conducted in compliance with the protocol, GCP guidelines, and applicable regulatory requirements.

5.2.4. Benefit/Risk Assessment

Based on the experience of rusfertide dosing in nonclinical species, Phase 1 studies and in the Phase 2 trials there appear to be no activities of the molecule that are not closely related to the proposed mechanism of action. No malignancies have been detected in various nonclinical studies of rusfertide in normal animals. However, benign and malignant squamous cell tumors were observed in a rasH2 transgenic mouse, which has been developed as an alternative to the lifetime mouse bioassay to predict the carcinogenic potential of chemicals.

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The risk of carcinogenicity for rusfertide continues to be evaluated in nonclinical and clinical studies due to the known enhanced risk of malignancy in PV patients and to discern if there is any increased risk over baseline risk due to rusfertide. To assess this risk, clinical trials of rusfertide have enhanced monitoring for development of cancers.

Immunologic responses to rusfertide have not been observed in nonclinical species, however administration of rusfertide to humans carries theoretical liabilities (immunologically based responses) associated with the systemic administration of a peptide. Rusfertide was well tolerated, with the most common adverse events (AEs) being injection site reactions (primarily transient erythema, pain, and pruritus). Rusfertide may cause anemia or increased platelet counts. Thus, rusfertide is expected to be well tolerated in the present study. However, clinical experience with rusfertide is limited and investigators must be vigilant to identify previously unknown risks of rusfertide.

In nonclinical studies high doses (>0.6 mg/kg) of rusfertide cause anemia by restricting iron availability for erythropoiesis. Mild to moderate anemia has been reported in participants treated with rusfertide. The anemia improved after dose adjustment. Thrombocytosis has developed in some participants treated with rusfertide but there have been no clinically significant related complications. Complete blood counts are performed routinely throughout this study to monitor for development of anemia or thrombocytosis.

Nonclinical and clinical observations suggest that rusfertide may restrict erythropoiesis in patients with PV. Restricted erythropoiesis could reduce or possibly eliminate the requirement

for phlebotomy to maintain hematocrit below 45%. The international guidelines recommend maintaining a hematocrit of less than 45% to minimize risk for morbidity and mortality (due to cardiovascular, cerebrovascular and thrombotic events) in PV patients. Patients with PV are typically severely iron deficient due to repeated phlebotomy and this iron deficiency results in substantial morbidity, including fatigue and cognitive defects. The rising serum ferritin levels in PV patients treated with rusfertide suggest that rusfertide may be effective for reversing iron deficiency.

The balance of the nonclinical and clinical data to date suggests that rusfertide has a safety profile that supports its continued clinical evaluation in PV. In Phase 2 studies rusfertide has demonstrated the ability to decrease phlebotomy requirements and maintain hematocrit less than 45% while decreasing symptoms of iron deficiency in patients with uncontrolled erythrocytosis despite phlebotomy and cytoreductive therapy. Thus, the potential benefits appear to outweigh the potential risks of rusfertide and clinical testing of rusfertide for PV is appropriate.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of rusfertide may be found in the IB.

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6. OBJECTIVES AND ENDPOINTS

6.1. Objective

To evaluate the safety and efficacy of rusfertide in participants with polycythemia vera in maintaining hematocrit control.

6.2. Endpoints

6.2.1. Efficacy Endpoints

Primary endpoint:

The proportion of participants achieving a response starting at Week 20 through Week 32 (inclusive) who receive rusfertide compared to placebo. Response is defined as absence of phlebotomy eligibility.

Phlebotomy eligibility is defined as **either**:

- a confirmed hematocrit ≥45% and that is at least 3% (absolute) higher than the baseline hematocrit. Confirmation is defined as 2 consecutive hematocrit assessments that are ≥45% and at least 3% higher than the baseline hematocrit.

or

- a hematocrit ≥48%.

Hematocrit values from each clinical site's local laboratory will be used for the primary endpoint.

Key secondary endpoints: Comparison of rusfertide to placebo

1. Mean number of phlebotomies between Week 0 through Week 32 (inclusive).
2. Proportion of participants with all hematocrit values <45% between Week 0 through Week 32 (inclusive). A single hematocrit value ≥45% is allowed. Hematocrit values from each clinical site's local laboratory will be used for this endpoint.
3. Mean change from baseline at end of Part 1a (Week 32) in the Patient Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a total T-score.
4. Mean change from baseline at end of Part 1a (Week 32) in the MFSAF TSS7 at Week 32. The weekly TSS7 at Week 32 will be calculated by averaging daily TSS7 over a 7-day interval leading to Week 32 (inclusive).

Other secondary endpoints:

Part 1a - Week 0 through Week 32 (both inclusive):

Comparison of rusfertide to placebo during randomized, double-blind, placebo-controlled, add-on parallel phase

PV-focused PRO-related secondary endpoints in participants with moderate or severe symptoms:

- Mean change from baseline at end of Part 1a (Week 32) in the PROMIS Fatigue Short Form 8a total T-score among participants who have moderate or severe symptoms at baseline.
- Mean change from baseline at end of Part 1a (Week 32) in the MFSAF Total Symptom Score-4 items (TSS4) among participants who have moderate or severe symptoms at baseline. TSS4 is the sum of 4 items of the MFSAF (fatigue, itching, night sweats, and abdominal discomfort). The weekly TSS4 at Week 32 will be calculated by averaging daily TSS4 over a 7-day interval leading to Week 32 (inclusive).
- Mean change from baseline at end of Part 1a (Week 32) in the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Problems with Concentration among participants who have moderate or severe symptoms at baseline.
- Proportion of participants with a meaningful within-person change at Week 32 in the PROMIS Fatigue SF 8a total T-score, MFSAF TSS4, and MPN-SAF problems with concentration among participants who have moderate or severe symptoms at Baseline.

Other PRO-related secondary endpoints

- Mean change from baseline at each scheduled assessment in individual questions and the total fatigue T-score based on PROMIS® Short Form 8a.

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- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MFSAF v4.0.
- Proportion of participants with a meaningful within-person change at Week 32 in the PROMIS Fatigue SF 8a total T-score, MFSAF TSS4, and MPN-SAF problems with concentration.
- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MPN-SAF TSS 10.
- Mean change from baseline in Patient Global Impression of Severity (PGI-S) at each scheduled assessment.
- Proportion of participants with at least one unit improvement in the PGI-S from baseline, that is, a ≥ 1 point decrease in the PGI-S, for example, a change from "Moderate (2)" to "Mild (1)" or "Mild (1)" to "None (0)" at each scheduled visit.
- Proportion of participants with a rating on the PGI-C of either "much better" or "a little better" at each scheduled assessment.
- Mean PGI-C at each scheduled assessment.
- Mean change from baseline in the individual domain scores and the total EORTC QLQ-C30 score at Week 32.

Hematocrit and Phlebotomy-related secondary endpoints

- Median time to first hematocrit ≥45% after randomization.
- Proportion of participants with at least one hematocrit ≥48%.
- Proportion of participants who maintain absence of phlebotomy eligibility.

Part 1a+1b: Week 0 through Week 52

- Proportion of participants originally randomized to rusfertide achieving absence of phlebotomy eligibility (durable response) for ≥ 52 weeks.
- Median time to first hematocrit ≥45% during Part 1b excluding Part 1a.
- Median time to first phlebotomy during Part 1b excluding Part 1a.

6.2.2. Safety Endpoints

Part 1a+1b+2+3: Week 0 through End of Study

- Frequency distribution will be presented for TEAEs, serious TEAEs and AEs of special interest (AESI).
- Clinical safety laboratory tests, physical examination, vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate) and 12-lead electrocardiogram (ECG) findings will be summarized as applicable.

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6.2.3. PK/PD Endpoints

Sparse blood sampling will be conducted for PK. A population analysis of the rusfertide concentrations will be examined. The relationship between efficacy and rusfertide exposure (AUC, C_{trough}, and C_{max}) will be explored. Participant characteristics such as gender, age, weight and cytoreductive treatment may be considered as covariates in the analyses.

PD endpoints are serum iron, ferritin, transferrin and transferrin saturation (TSAT).

6.2.4. Exploratory Biomarkers of Interest

Exploratory biomarkers to be assessed will include, but are not limited to, the following:

- Erythropoietin
- Hepcidin, IL-6, fibrogen d-dimer.
- JAK2 mutation burden
- Additional markers of inflammation, hematopoiesis, and coagulation may be included based on the most recent scientific literature at the time of analysis.

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7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase 3, multicenter, global randomized trial that compares the efficacy and safety of rusfertide compared to placebo when added on to current therapy for PV (Figure 1). The study population is participants with PV who require frequent phlebotomies to control their hematocrit. Approximately 250 participants will be randomized.

This Phase 3 study in participants with polycythemia vera is designed as follows:

- Part 1a: randomized, double-blind, placebo-controlled, add-on parallel-group period for 32 weeks. Participants will be randomized 1:1 in a blinded fashion to 32 weeks of add-on rusfertide or placebo treatment. Rusfertide or placebo will be added-on to each participant's ongoing therapy for PV. Randomization will be stratified by ongoing PV therapy.
- Part 1b: open-label treatment phase during which all participants who complete Part 1a successfully will receive rusfertide for 20 weeks (Week 32 through Week 52).
- Part 2: long term extension for 104 weeks (Week 52 through Week 156) during which all participants who complete Part 1b will continue to receive rusfertide.
- Part 3: Rusfertide treatment extension for participants who complete Part 2. Participants who complete Part 2 may be eligible for Part 3 if, in the opinion of the investigator, they are continuing to derive benefit from rusfertide and:

– do not have access on the commercial market following local commercial availability under the standard pricing and reimbursement model in a country

or

– cannot obtain rusfertide through a post-trial access (PTA) program.

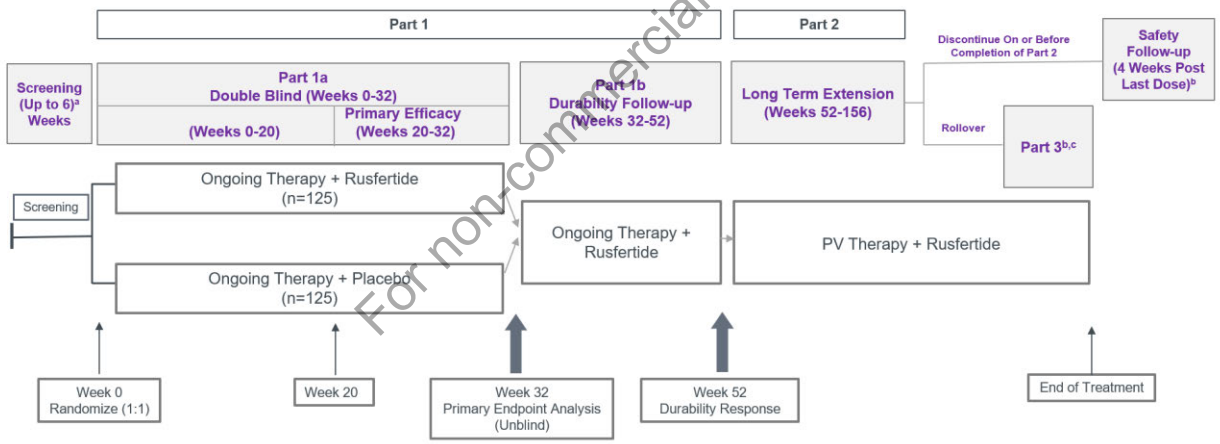
During Part 3, participants will come to the clinic every 12 weeks. The dose of cytoreductive agents may be adjusted for either safety or efficacy; additionally, participants may begin new cytoreductive therapy in Part 3.

Weeks 32, 52, and 156 are transition visits between study parts; week ranges are inclusive and refer to the scheduled study week/visit label.

Access to rusfertide following completion of this trial will be determined by local regulatory requirements and available access mechanisms (for example, commercial availability/reimbursement, a PTA program, or other sponsor-determined access mechanism, as applicable).

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Figure 1: Study Design PTG-300-11



[a] Phlebotomy history for up to 52 weeks
[b] Participants who permanently discontinue rusfertide at or before Week 156 and do not enter Part 3 will be contacted approximately 6 and 12 months after their last dose to assess the occurrence of any new cancer events. Participants who enter Part 3 will have safety events collected through the EOS Part 3 visit, with no additional protocol-required post-dose contacts after EOS Part 3.
[c] A 4-week safety follow-up visit is not required for subjects in Part 3.

7.1.1. Investigational Treatment

In Part 1a, participants are randomized (1:1) to:

- Treatment Arm 1: Rusfertide added to ongoing PV therapy at randomization.
- Treatment Arm 2: Placebo added to ongoing PV therapy at randomization.

In Part 1b, all participants receive open label rusfertide added to the ongoing PV therapy at randomization.

In Part 2 and Part 3, all participants receive open label rusfertide. The ongoing PV therapy may be changed at the investigator's discretion.

7.1.2. Treatment Duration Including Post-Treatment Safety Follow-up

Individual participants will participate in this study as follows:

- Screening: Up to 6 weeks
- Part 1a: Double-blind: 32 weeks (Week 0 to Week 32)
- Part 1b: Open-label: 20 weeks (Week 32 to Week 52)
- Part 2: Long-term extension: 104 weeks (Week 52 to Week 156)
- Post-treatment safety follow-up: 4 weeks after last dose of study drug for participants who do not continue into Part 3
- Part 3: Rusfertide treatment extension: End of Part 2 (Week 156) to End of Study

Post-Treatment Safety Follow-Up:
Participants who permanently discontinue rusfertide at or before Week 156 and do not enter Part 3 will be contacted (for example, by telephone) approximately 6 and 12 months after their last dose to assess the occurrence of any new cancer events. Participants who enter Part 3 will have safety events collected through the EOS Part 3 visit, with no additional protocol-required postdose contacts after EOS Part 3.

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7.1.3. Treatment Blinding

Treatment assignment in Part 1a will be blinded to investigators, participants and all study personnel. In Part 1b, all participants will receive rusfertide. After all Week 32 assessments are completed as outlined in Table 6, IxRS will assign treatment dose to each participant. Assigning treatment dose at the beginning of Part 1b may potentially unblind treatment assignment in Part 1a. In Part 2 and Part 3, all participants will receive rusfertide.

7.2. Rationale for the Study Design

The participants selected for this study have poor hematocrit control as evidenced by their requirement for frequent phlebotomies while receiving standard therapy for PV. The study's primary endpoint of phlebotomy eligibility is based on hematocrit, which is a laboratory measurement that is not subject to bias. However, treatment is blinded for the first 32 weeks to allow assessment of endpoints, such as patient reported outcomes, that could be subject to bias.

This study has three parts. In Part 1a, participants are randomized 1:1 to treatment with rusfertide or placebo which are added on to the participant's ongoing PV therapy at randomization for 32 weeks. Part 1b is open label treatment with rusfertide in all participants. This allows assessment of durability of response in participants who were randomized to rusfertide in Part 1a and allows initial assessment of rusfertide's efficacy in participants who were randomized to placebo in Part 1a. Part 2 extends open-label treatment with rusfertide for an additional 104 weeks to obtain data on long-term safety of treatment with rusfertide. Part 3 extends open-label treatment with rusfertide for participants who have completed Part 2 and, in the opinion of the investigator, are continuing to derive benefit from rusfertide treatment.

Two formulations have been used in clinical trials conducted in participants with PV. In the Phase 2 trials (PTG-300-04 and PTG-300-08), rusfertide was formulated as a liquid formulation dispensed into a 1 mL PFS at 0.5 mL or 1.0 mL fill volume for SC administration. For the Phase 3 trial (PTG-300-11), an LPF was developed for improved product stability and was supplied in a glass vial with an accompanying diluent for reconstitution. The LPF was also used in the long-term extension trial (PTG-300-21), which enrolled participants who completed the Phase 2 trial PTG-300-04.

In the Phase 2 study PTG-300-04, the starting dose was 20 mg of the Phase 2 liquid formulation per week and the majority of participants were dosed with 40 to 60 mg per week, with some participants requiring higher doses of up to 120 mg per week, to maintain a hematocrit <45%. The recommended starting dose of rusfertide in Trial PTG-300-11 is 19 mg of the LPF formulation administered subcutaneously. In addition, a dose of 9.5 mg is available for those participants who may require a lower dose. All doses will be individually titrated (increased or decreased) as necessary to maintain the hematocrit less than 45%. The maximum daily dose of rusfertide is 82 mg, which is similar to the maximum daily dose in the Phase 2 trials (80 mg). The maximum total weekly dose of rusfertide is 108 mg/week in this trial. Compared to the Phase 2 liquid formulation, an initial preliminary analysis indicated that the lyophilized powder formulation (LPF) used in this Phase 3 trial results in an approximately 25% higher drug exposure. However, dose titration ensures that each participant receives the appropriate dose of study drug.

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This study uses an “add on” design because rusfertide reduces erythropoiesis selectively. Some participants with PV have elevated white blood cells (WBC) or platelets in addition to elevated hematocrit. The “add on” design allows these participants to receive standard cytoreductive therapy to control WBC and/or platelets and to receive rusfertide/placebo if cytoreductive therapy does not control hematocrit adequately. The dose of cytoreductive therapy in Part 1a and Part 1b may be decreased for safety but may not be increased and initiation of cytoreductive therapy is not allowed for efficacy including control of hematocrit, elevated platelets and/or WBC. Increasing the dose of cytoreductive therapy may decrease the number of phlebotomy eligible events thereby decreasing the study’s ability to detect a true treatment difference between rusfertide and placebo and potentially causing erroneous attribution of benefit to study treatment (rusfertide or placebo) when benefit resulted from the cytoreductive therapy dose increase.

Participants in Parts 1a, 1b, and 2 are evaluated 4 weeks after their last dose of study drug to evaluate post-treatment safety. The purpose of Part 3 is to make rusfertide available to participants who are deriving benefit from the drug until it is either commercially available or through a PTA program. Key safety information will be collected during the course of Part 3.

7.3. Number of Participants

Approximately 250 participants will be randomized in this study.

7.4. Early Trial or Site Closure

The sponsor may suspend or terminate part of the trial, or the trial in its entirety, at any time for any reason. The sponsor reserves the right to close a trial site at its sole discretion. Sites will be closed upon trial completion.

Sites may be closed by the sponsor due to failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines; inadequate or no recruitment (evaluated after a reasonable amount of time); inclusion of the total number of participants earlier than expected, or other reasons not listed herein.

The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

Please see Section 17.6 (Early Site Closure or Trial Termination) for criteria and responsibilities related to early site closure or trial termination

7.5. COVID-19 and Other Disaster Management

See Appendix 4 for a description of actions that may be taken during the coronavirus disease 2019 (COVID-19) pandemic or other disasters to manage operational disruptions, to ensure participant safety and to preserve the integrity of the study.

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8. ACCESS TO TRIAL INTERVENTION AFTER END OF TRIAL

8.1. PTA

Access to rusfertide following completion of this trial will be determined by local regulatory requirements and available access mechanisms (for example, commercial availability/reimbursement, a PTA program, or other sponsor-determined access mechanism, as applicable).

9. SELECTION OF PARTICIPANTS

The study population is female or male participants with PV who require frequent phlebotomies to control their hematocrit.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

9.1. Participant Inclusion Criteria

Participants must meet ALL of the following inclusion criteria:

1. Male and female participants aged 18 (or the minimum country specific age of consent if >18) years or older.
2. Participant understands the study procedures, is willing and able to adhere to study requirements and agrees to participate in the study by giving written informed consent.
3. Meet revised 2016 World Health Organization (WHO) criteria for the diagnosis of polycythemia vera (Appendix 1).
4. Phlebotomy requiring defined as **ALL** of the following:
   a. At least 3 phlebotomies due to inadequate hematocrit control in 28 weeks before randomization or at least 5 phlebotomies due to inadequate hematocrit control in 1 year before randomization, **and**
   b. Last phlebotomy due to inadequate hematocrit control within 3 months before randomization, **and**
   c. No phlebotomy within 6 days prior to randomization (do not include day of phlebotomy and day of randomization in the 6-day count).

   Note: Phlebotomies performed within an 8-day period will be counted as a single phlebotomy.
5. CBC values immediately prior to randomization:
   a. Hematocrit <45%,
   b. WBC 4000/µL to 20,000/µL (inclusive), and
   c. Platelets 100,000/µL to 1,000,000/µL (inclusive).
6. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
7. Women of childbearing potential (WOCBP) agree to use medically acceptable contraception (<1% annual failure rate) during the study and for 30 days after the last dose of study drug (Appendix 2).
8. A female participant must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 30 days after receiving the last dose of study medication.
9. Men with partners of childbearing potential agree to use medically acceptable contraception (<1% annual failure rate) during the study and for 90 days after the last dose of study drug (Appendix 2). In addition, men must use a condom during the study and for 90 days after the last dose of study drug regardless of the partner's childbearing potential.
10. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last dose.

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11. Participants receiving cytoreductive therapy at randomization must be on a stable PV therapy regimen as follows:

    a. Hydroxyurea - at least 2 months
    b. JAK inhibitor - at least 2 months
    c. Interferon - at least 6 months.

    Note: A "stable dose regimen" of cytoreductive therapy does not mean an unchanged dose regimen. Temporary adjustments in dose regimen or temporary suspension of dosing are allowed. However, the total weekly dose of hydroxyurea and JAK inhibitor or total monthly dose of interferon **may not be higher at randomization than the dose at the beginning of the pre-randomization** observation period. The pre-randomization observation period is 2 months for hydroxyurea and JAK inhibitor and 6 months for interferon.

12. Participants treated with phlebotomy alone at randomization must have stopped:

    a. Hydroxyurea at least 2 months before screening
    b. JAK inhibitor at least 2 months before screening
    c. Interferon at least 6 months before screening.

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9.2. Participant Exclusion Criteria

Participants must not meet ANY of the following exclusion criteria to be enrolled:

1. Clinically meaningful laboratory abnormalities at Screening including, but not limited to:

    a. Estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2.5 × upper limit of normal (ULN)
    c. Total bilirubin >1.5 × ULN.

    Note: Screening laboratory tests with abnormal results (if considered by the investigator to be transient and inconsistent with the participant's clinical condition) may be repeated within the screening window to confirm abnormal results. If results return to protocol acceptable limits within the screening period, the participant may enter the study. Use local labs for complete blood count (CBC) and use central labs for all other eligibility lab tests.

2. Participants who require phlebotomy at hematocrit levels lower than 45%.
3. Pregnant or lactating females.
4. Clinically significant thrombosis (for example, deep vein thrombosis or splenic vein thrombosis) within 2 months prior to randomization.
5. Active or chronic bleeding within 2 months prior to randomization.

6. Meets the criteria for post-polycythemia vera myelofibrosis as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT).
7. Any infection requiring systemic therapy within 1 month of dosing except controlled HIV, hepatitis B, and hepatitis C. Prophylactic therapies are allowed.
8. Any serious or unstable medical condition (for example, poorly controlled HIV infection) or uncontrolled psychiatric condition as judged by the investigator that would impair the participant's ability to participate in the study.
9. Major surgical procedure within 2 months prior to randomization unless the participant has fully recovered from surgery or planned major elective surgery during the study.
10. History of invasive malignancies within the last 5 years, except
    a. localized cured cancer (for example, prostate cancer and cervical cancer)
    b. localized cured in situ or stage 1 squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or in situ melanoma of the skin.
11. Participants with 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 the required dermatology examination at screening unless the cancer is adequately treated (that is, treatment that is expected to be curative, such as Mohs surgery) before randomization. Note: Suspicious lesions should be biopsied and results available before randomization.
12. Participants with active alcohol or drug addiction that would interfere with their ability to comply with study requirements.
13. Participants who do not complete at least 4 days of Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) assessments within 1 week prior to randomization.
14. Receipt of an investigational agent within 2 months or 5 half-lives, whichever is longer, prior to randomization.
15. Received busulfan, pipobroman or ^{32}Phosphorus within 7 months prior to screening.
16. Participants with hypersensitivity to rusfertide or to any of the excipients or placebo.
17. Participants with any lesion or mass detected by physical examination or imaging during screening that is suspicious for malignancy unless evaluated and assessed to be not malignant.

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9.3. Stopping Rules and Participant Withdrawal Criteria

9.3.1. Study Stopping Rules

Sequential boundaries will be used to monitor development of human cancer (Ivanova 2005) in evaluable participants. This is a Pocock-type stopping boundary that yields the probability of

crossing the boundary at 0.05, assuming the human cancer development rate in this population to be 0.08 (Khanal 2016, Masarova 2016).

If a cancer-development event is observed in the evaluable population, the sponsor (or sponsor's medical monitor/designee) will be informed and will perform an ad hoc medical review in conjunction with the investigator's assessment.

A cancer-development event will contribute toward the observed number of cases for the Pocock-type stopping boundary if it is assessed as possibly related or related to rusfertide by either the investigator or the sponsor.

If the total number of such cases observed in the rusfertide-treated group is equal to or exceeds "x" out of "n" evaluable participants during the study duration (Table 2), accrual and dosing will be halted pending further sponsor's review.

If the study is halted due to safety concerns, or if the study stopping rules described in this section are triggered, the study can only be restarted after regulatory authority approval via a substantial amendment.

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Table 2: Pocock Boundary for N=125 that Yields Probability of Stopping = 0.05 Assuming Cancer Development Rate in This Population = 0.08

n (# of evaluable participants)	1	2	3-6	7-11	12-17	18-23	24-30
x (# of observed related cancer cases)	-	2	3	4	5	6	7
n (# of evaluable participants)	31-38	39-45	46-53	54-61	62-70	71-78	79-87
x (# of observed related cancer cases)	8	9	10	11	12	13	14
n (# of evaluable participants)	88-96	97-104	105-113	114-123	124-125		
x (# of observed related cancer cases)	15	16	17	18	19		

9.3.2. Participant Stopping Rules

Participant participation in the study must stop for any of the following reasons:

- Stage 2 or higher basal cell carcinoma
- Stage 2 or higher squamous cell carcinoma of the skin
- New cancer requiring therapy that would interrupt study drug for more than 4 weeks
- Recurrence of cancer except for local recurrence of inadequately treated non-melanomatous skin cancer. Inadequate treatment includes treatment that is not intended to be curative and treatment that leaves residual tumor.
- Persistent (confirmed at least 8 weeks later) increase in leukocytes (>$25x10^9$/L with at least a 50% increase in baseline leukocyte count from Day 1 of Week 0) in either Part 1a or Part 1b
- Persistent (confirmed at least 8 weeks later) increase in platelets (>$1500x10^9$/L) in either Part 1a or Part 1b.

Participants with persistently elevated leukocytes or platelets in Part 2 or Part 3 are allowed to remain in the study provided the investigator begins cytoreductive therapy or adjusts concurrent cytoreductive therapy to control the elevated counts.

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9.3.3. Participant Withdrawal Criteria

A participant may choose to withdraw at any time. A participant should be withdrawn if the investigator or sponsor thinks withdrawal is in the participant's best interest.

A participant must be withdrawn if:

- Participant requests withdrawal from the study.
- Participant is noncompliant with study drug administration or study procedures.
- Participant becomes pregnant.
- Clinically significant adverse events which prevent continuation of the study medication, as determined by the investigator.
- Participant starts a new cytoreductive therapy in either Part 1a or Part 1b.
- Participant receives cytoreductive therapy other than hydroxyurea, interferon, ruxolitinib or an approved JAK inhibitor.
- Clinically significant laboratory values which require change in PV therapy, as determined by the investigator.
- Any CTCAE Grade 3 or Grade 4 toxicity, when the investigator, in consultation with the medical monitor, considers that it is in the participant's best interest to discontinue treatment with study drug.

- Participant starts an experimental therapy.
- Participant's treatment is unblinded before the participant completes Part 1a.
- Lost to follow-up (a participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits).

10. TREATMENT OF PARTICIPANTS

10.1. Randomization

Participants will be stratified by ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other) and randomized 1:1 to receive rusfertide or placebo for 32 weeks. Study drug (rusfertide or placebo) will be added on to each participants' ongoing PV treatment at randomization.

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10.2. Blinding and Unblinding

During Part 1a of the study, the sponsor, contract research organizations (CROs), medical monitors, investigator, site pharmacist (or designee), site personnel involved in study conduct, and participants will remain blinded to study medication assignment. Treatment assignment will be implemented using an interactive response system (IxRS).

Treatment assignment for an individual participant in Part 1a may be made available to the investigator (or designee) only in the event of a medical emergency or an AE that necessitates identification of the clinical trial material for the welfare of that participant (see Section 14.6). If an investigator unblinds a participant's treatment assignment before the participant completes Part 1a of the study, the participant will be removed from the study.

Participants who complete Part 1a will continue to Part 1b. Since a participant randomized to placebo group in Part 1a will receive 19 mg of active drug, the site and participant will be unblinded. Because of potential unblinding at the start of Part 1b, all required assessments at Week 32 must be completed prior to continuing to Part 1b.

Treatment in Parts 1b, 2, and 3 is not blinded.

10.3. Treatment Administration

10.3.1. Description of Study Drug

Study drug will be provided by Takeda for this study.

Rusfertide will be provided in a convenience kit containing the drug as a lyophilized powder in a glass vial with an accompanying vial or syringe of diluent for reconstitution.

Identical-appearing placebo will be provided as a lyophilized powder in a glass vial with an accompanying vial or syringe of diluent for reconstitution.

10.3.2. Study Drug Injection

Study drug is injected subcutaneously. Recommended injection sites are SC tissue in abdomen (5 cm away from the navel) or thighs. Injection sites should be rotated between injections.

Participants and/or their caregivers will be trained to administer study drug for home use. Initially, all doses should be administered in the clinic by a trained health care practitioner until the participant or caregiver demonstrates the ability to successfully administer study drug or arrangements have been made for a healthcare professional to administer study drug outside the clinic. Participants will be assessed for approximately 30 minutes for safety observations after the first dose of study drug. To ensure participants continue to inject study drug correctly, sites should observe the participant (or care giver) administer study drug when the participant is in the clinic on a day of study drug administration.

Detailed instructions for preparing and injecting rusfertide are provided in the Pharmacy Manual and in a handout for participants.

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10.4. Study Drug Dosing Guidelines

10.4.1. Study Drug Dosing

In Part 1a, study drug refers to rusfertide or placebo; in Part 1b, Part 2, and Part 3, study drug refers to rusfertide.

Study drug is provided in dose strengths of 9.5 mg, 19 mg, 28 mg, 41 mg and 54 mg. Doses above 54 mg require two injections of study drug. Study drug is injected subcutaneously (Section 10.3.2). Recommended injection sites are SC tissue in abdomen (5 cm away from the navel) or thighs. Injection sites should be rotated between injections. Table 3 describes the dose administration instructions.

In Parts 1a and 1b the allowed dose levels of rusfertide are 9.5 mg, 19 mg, 28 mg, 41 mg and 54 mg, 69 mg, and 82 mg. **Study drug must be administered once per week and the maximum dose administered in one day is 82 mg in Parts 1a and 1b**. For dose levels above 54 mg, study drug should be administered as two injections at different sites at least 5 cm apart on the same day.

In Part 2 and Part 3, dose levels include 9.5 mg, 19 mg, 28 mg, 41 mg, 54 mg, 69 mg, 82 mg, 95 mg, and 108 mg. The **maximum dose administered in one day is 82 mg and the maximum total weekly dose is 108 mg in Part 2 and Part 3.** Similar to Part 1a and 1b, doses levels above 54 mg will require two injections.

The dosing schedule is weekly, as shown in Table 3. Participants who were on alternative dosing schedules (for example, every 2 weeks dosing, intermediate dosing, alternating dosing) prior to implementation of Protocol Amendment 7 may continue their existing schedule, based on investigator's discretion.

Table 3 Administration Instructions

Weekly Dose	Administration Instructions	Additional Instructions
9.5 mg	Single injection to achieve weekly dose.	
19 mg		
28 mg		
41 mg		
54 mg		
69 mg	Inject 28 mg and 41 mg on the same day to achieve weekly dose.	
82 mg	Inject 2 doses of 41 mg on the same day to achieve weekly dose.	
95 mg	Inject 54 mg on Day 1 and 41 mg on Day 4 or 5 to achieve weekly dose.	This administration is permitted only in Part 2 and Part 3.
108 mg	Inject 54 mg on Day 1 and 54 mg on Day 4 or 5 to achieve weekly dose.	

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Placebo will be administered as described for rusfertide in Part 1a.

10.4.1.1. Starting Doses: Parts 1a, 1b, 2, and 3

10.4.1.1.1. Part 1a

Part 1a is double blind. The starting dose is 19 mg rusfertide or placebo administered SC once a week for all participants.

10.4.1.1.2. Part 1b

Part 1b is open label. Participants randomized to rusfertide continue to receive rusfertide SC once a week at their current dose unless dose adjustment is required. Participants randomized to placebo start rusfertide treatment at the 19 mg dose level administered SC once a week.

10.4.1.1.3. Part 2 and Part 3

All participants continue to receive rusfertide at their current dose unless dosing regimen adjustment (for example, change in dosing schedule to two times a week or change in dose level), is required.

10.4.1.2. Dosing Schedule

10.4.1.2.1. Part 1a and Part 1b

Study drug is administered subcutaneously once a week. Study drug may be administered as one or two injections on the same day.

10.4.1.2.2. Part 2 and Part 3

Study drug is typically administered SC once a week (see Table 3 for administration instructions). Study drug may be administered SC twice weekly for weekly doses above 82 mg as outlined in Table 3. Participants who were on alternative dosing schedules (for example, every 2 weeks dosing, intermediate dosing, alternating dosing) prior to implementation of Protocol Amendment 7 may continue their existing schedule per Section 10.4.2, based on investigator's judgment.

10.4.1.3. Frequency of Dose Adjustment

It normally takes 2 to 4 weeks to assess the impact of a change in dose. It is recommended that the dose of rusfertide not be changed more often than every 2 weeks.

10.4.1.4. Dose Increase for Hematocrit Control

The dose should be adjusted to maintain hematocrit <45%.

- In order to reduce the risk of day-to-day variation resulting in hematocrit values >45%, it is recommended that the dose of study drug be increased when
  - the hematocrit is ≥43% OR
  - the absolute hematocrit increases by ≥ 2% compared to values obtained over the previous 2 to 4 weeks and the hematocrit is anticipated to exceed 43%.
- After a minimum of 2 weeks at the current weekly dose, a dose increase may be considered according to Table 4 and based on medical judgement to reduce hematocrit to the desired level below 45% or to maintain hematocrit at the desired level. After each dose increase, the dose should remain stable for at least 2 weeks before considering an additional increase.

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Table 4 Recommended Rusfertide Dose Increase to Reduce or to Maintain Hematocrit Below 45%

Current Weekly Dose	Increase Weekly Dose to
9.5 mg	19 mg
19 mg	28 mg
28 mg	41 mg
41 mg	54 mg
54 mg	69 mg
69 mg	82 mg
82 mg	95 mg
95 mg	108 mg

10.4.1.5. Dose Decrease

For participants with CTCAE Grade 2 and higher anemia, the dose may be decreased. For participants with study drug-related Grade 3 or higher toxicity (hematological and non-hematological), the dose must be decreased. Decrease dose according to Table 5 below:

Table 5 Recommended Rusfertide Dose Decrease for Patients Experiencing Grade ≥2 Anemia or for Drug-Related Grade ≥3 Toxicities

Current Weekly Dose	Decrease Weekly Dose to
108 mg	95 mg
95 mg	82 mg
82 mg	69 mg
69 mg	54 mg
54 mg	41 mg
41 mg	28 mg
28 mg	19 mg
19 mg	9.5 mg
9.5 mg	Discontinue treatment

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10.4.2. Rusfertide Dosing in Part 2 and Part 3

Rusfertide is routinely administered once weekly for doses up to 82 mg, and twice weekly for doses above 82 mg, as outlined in Table 3. Patients who were on other dosing schedules (for example, every-2-weeks dosing, intermediate dosing, alternating dosing) prior to the implementation of Table 3 in Protocol Amendment 7 may continue their existing dosing schedule based on the investigator's clinical judgment. For participants continuing on alternate dosing schedules (for example, every-2-weeks dosing), see Section 10.5.1 for instructions on management of delayed doses.

10.5. Treatment Delay or Interruption

10.5.1. Delayed Dosing

See recommended procedures below for managing dose delays:

- Dosing once a week
  - Dose delay 1 to 4 days: Take missed dose immediately. Then resume normal regular schedule.
  - Dose delay >4 days: Take missed dose immediately. Take the next dose 3 days later. Then resume the normal regular dosing schedule.
- Dosing two times a week (in Part 2 and Part 3 only)

  - Dose delay 1-2 days: Take missed dose immediately. Take the next dose 3 days later. Then resume the normal dosing schedule.
  - Dose delay >2 days: Skip the dose. Continue normal dosing schedule.
- Dosing every 2 weeks (in Part 2 and Part 3 only and for participants with existing every 2 weeks dosing before the implementation of Protocol Amendment 7)
  - Take missed dose immediately, then resume normal regular schedule. There should be at least 3 days between taking the missed dose and resuming the normal schedule. If necessary, delay resuming the normal schedule for 1-3 days (for delayed-dose instructions for alternate schedules, see Section 10.5.1.

10.5.2. Treatment Interruption

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may or may not be due to study drug. The investigator may withhold study drug at any time if there is concern about participant safety.

For Parts 2 and 3, continued study participation following a treatment interruption of more than 12 weeks should be discussed with the sponsor.

If the investigator decides to re-start treatment with study drug, then dosing should resume as follows:

- If the event causing dose interruption is not related or unlikely related to study drug, then resume study drug at the last dose before dose interruption.
- If the event causing dose interruption is possibly related or related study drug, then resume study drug at one dose level (Section 10.4.1.5) below the dose level that resulted in dose interruption.

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10.6. Concurrent Therapy for PV

Participants will continue the PV therapy they were receiving at randomization.

10.6.1. Phlebotomy Only

Participants should undergo a phlebotomy if **either**:

- their confirmed hematocrit is ≥45% and that is at least 3% (absolute) higher than the baseline hematocrit.

  Confirmation is defined as 2 consecutive hematocrit assessments that are ≥45% and at least 3% higher than the baseline hematocrit.

or

- a hematocrit ≥48%.

10.6.2. Cytoreductive Therapy

Allowed cytoreductive therapies are hydroxyurea, interferon, ruxolitinib and other JAK inhibitors.

- In Part 1a and Part 1b, participants should continue their ongoing cytoreductive therapy. The dose of cytoreductive therapy may be decreased or stopped for safety but cannot be increased above the Week 0 dose for efficacy (for example, to control hematocrit, platelets or leukocytes levels) and participants cannot start new cytoreductive therapy. If the dose is decreased for safety purposes, the dose may subsequently be increased up to the level at Week 0.
- In Part 2 and Part 3, the dose of cytoreductive therapy may be decreased or stopped for safety and may be increased for efficacy including to control hematocrit, platelets or leukocytes levels. Participants may also begin new cytoreductive therapy in Part 2 and Part 3.

10.7. Permitted Concomitant Therapy

Participants should receive appropriate care for PV including instructions on diet. Antiplatelet agents (for example, low-dose aspirin and clopidogrel) and anticoagulants (for example, vitamin K antagonists and novel oral anticoagulants) are permitted. Participants should receive full supportive care for any other underlying conditions. COVID-19 vaccination according to local standard of care is allowed and encouraged (Appendix 4).

Multivitamins without iron are preferred. However, multivitamins with iron are allowed if their content of iron is at or below the recommended daily dose of iron (for example, ≤20 mg/day).

Cytoreductive therapy is allowed as specified in Section 10.6.2.

Investigators should optimize anti-platelet therapy for participants with thrombocytosis. Anagrelide may be allowed for treatment of persistent thrombocytosis (for example, >1,000,000/mm^3) with prior approval of the medical monitor.

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10.7.1. Injection Site Reactions (ISRs)

Injecting rusfertide into exactly the same site may increase the severity of ISRs. To avoid injecting rusfertide into the same site, rusfertide injections should be a least 5 cm from the previous injection's site. Injections should also be rotated among different sites on the abdomen and thighs.

Over-the-counter antihistamines such as oral cetirizine or fexofenadine taken approximately 1 to 2 hours before injections appear to reduce the frequency and severity of ISRs. Over-the-counter analgesics such as acetaminophen may be used to treat injection site pain. Applying topical therapies such as corticosteroid creams, topical antihistamines, or ice to the injection site after each injection may be tried.

10.8. Prohibited Concomitant Therapy

Investigational agents must be discontinued at least 2 months or 5 half-lives prior to randomization and are not allowed during the study.

PV-specific therapies other than phlebotomy, hydroxyurea, interferon, ruxolitinib, and other JAK inhibitors are prohibited. Erythrocytapheresis is not allowed.

Iron supplementation may increase hematocrit. Iron supplementation at doses above 20 mg/day is not allowed. Investigator discretion should be used for dietary iron intake.

The investigator should review the participant's use of food supplements and natural remedies. If questions arise regarding the suitability of an agent, please contact the medical monitor.

10.9. Contraception

Women of child-bearing potential and men must use medically acceptable contraception (<1% annual failure rate) during the study and for 30 days for women and 90 days for men after the last dose of study drug. Medically acceptable methods of contraception that may be used by the participant and/or partner are listed in Appendix 2.

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10.10. Treatment Compliance

Assignment of rusfertide or placebo to the participant will be handled through an IxRS. All study medication will be assigned to the participant through the IxRS and a log of all received and dispensed medication will be maintained in the IxRS.

Participants will document use of study drug in the participant eDiary. The study site personnel will document compliance in the study source documents. In Part 3, participants are not required to complete eDiaries.

If the participant does not complete the eDiary appropriately for study drug administration or return used and unused study drug cartons, the site should:

- obtain as much information as possible as to the dosing of study drug. The information should be documented.
- retrain the participant.
- counsel participants on missed doses of study drug.

11. STUDY DRUG MATERIALS AND MANAGEMENT

Specific instructions about the storage, preparation, administration, and accountability of study drug are provided in the Pharmacy Manual.

11.1. Study Drug

11.1.1. Rusfertide

Rusfertide for injection is provided in a kit format. The kit for reconstitution contains one vial of rusfertide at a dose of 9.5 mg, 19 mg, 28 mg, 41 mg and 54 mg as a dry powder and a vial or syringe of diluent. Instructions for use are provided describing the reconstitution of the dry powder into a drug product solution. The nominal injection volume is 0.5 mL and contains the formula amount of rusfertide [redacted]

11.1.2. Placebo

Placebo is provided in an identical format as the rusfertide for injection kit for reconstitution. The nominal injection volume is 0.5 mL [redacted]

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11.2. Study Drug Packaging and Labeling

For Part 1a, rusfertide and placebo will be provided as a kit for reconstitution that is blinded as to study drug but not to dose level.

For Part 1b, Part 2, and Part 3, rusfertide will be provided as a kit for reconstitution that is labeled with the drug name and dose level.

11.3. Study Drug Storage

Study drug for injection reconstitution kits must be stored at 2 °C to 8 °C (35.6 °F to 46.4 °F), in the provided carton that provides protection from light, in a locked area with limited access.

11.4. Study Drug Accountability

Participants should return used and unused study drug cartons to the clinical site at each visit for drug accountability and compliance assessment.

A record will be maintained by the investigational sites that will account for all dispensing and return of any unused study drug.

Investigators will be fully responsible for the security, accessibility and storage of the study drug while it is at investigational sites. Investigators are also responsible for the education of study staff in the correct administration of the study drug.

11.5. Study Drug Handling and Disposal

Upon receipt of the study drug at the investigational site, the study drug must be stored at 2 °C to 8 °C in a secure location with limited access.

At the end of the study the study drug will be reconciled, and a copy of the record given to the study monitor. Upon completion of the study any surplus study drug will either be returned to the sponsor or be destroyed at the site upon receipt of written approval from Takeda. Evidence of destruction must be supplied to the study monitor.

Further information of the storage, preparation and administration of study drug will be provided in the Pharmacy Manual.

12. STUDY PROCEDURES

Study procedures should be completed as designated in the schedules of assessments (Table 6 [Part 1a]), Table 7 [Part 1b], Table 8 [Part 2], and Table 9 [Part 3]).

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Table 6: Schedule of Assessments for Study PTG-300-11: Part 1a

Assessment	Reference to Section	Screening	Part 1a Double Blind[a]								
Study Week[b]		Day -42 to -1	Wk 0 (Baseline)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32[c]
Administrative											
Informed Consent & HIPAA Authorization[d]	12.1.1	X									
Inclusion/Exclusion	8	X									
Demographics	12.1.2	X									
Medical history	12.1.2	X									
Family cancer history	12.1.2	X									
PV history	12.1.3	X									
Phlebotomy history	12.1.3	X									
Hematocrit history	12.1.3	X									
Cytoreductive therapy history	12.1.3	X									
ECOG Performance	12.1.4	X									
Dispensing and training of eDiary	12.2.1	X									
Eligibility confirmed	8		X								
Randomization in IxRS	12.2.2		X								
Participant contact reminder [e]	12.1.17	X[e]	X	X	X	X	X	X	X	X	X
Study Drug Administration											
Dispense study drug kits	10.3		X	X	X	X	X	X	X	X	X
Administer study drug	10.3		Weekly								
Complete eDiary for dosing	12.1.18.2		Weekly								

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Table 6: Schedule of Assessments for Study PTG-300-11: Part 1a

Assessment	Reference to Section	Screening	Part 1a Double Blind[a]								
Study Week[b]		**Day -42 to -1**	**Wk 0 (Baseline)**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32[c]**
Review eDiary for dosing compliance/retraining	10.10, 12.1.18.2			X	X	X	X	X	X	X	X
Safety Assessments											
Full physical examination (including weight)	12.1.7	X		X			X				X
Complete dermatologic examination[f]	12.1.8	X									X
Cancer screening counseling	12.2.1	X									
Height	12.1.6	X									
Problem-oriented Physical Examination	12.1.7	As Needed									
Vital signs	12.1.5	X	X	X	X	X	X	X	X	X	X
12-lead ECG PRE-dose only	12.1.9	X		X							X
12-lead ECG PRE-dose and POST-dose	12.1.9						X[g]				
Spleen size	12.1.14	X									X
Adverse events	14.2	X	X	X	X	X	X	X	X	X	X
Concomitant medications	10.7, 10.8	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments											
HIV, Hepatitis B & C	12.1.11		X								
Serum pregnancy test[h]	12.1.12	X									
Urine pregnancy test[h]	12.1.12		X	X	X	X	X	X	X	X	X

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Table 6: Schedule of Assessments for Study PTG-300-11: Part 1a

Assessment	Reference to Section	Screening	Part 1a Double Blind[a]								
Study Week[b]		Day -42 to -1	Wk 0 (Baseline)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32[c]
Urinalysis	12.1.10.3	X	X	X	X	X	X	X	X	X	X
CBC (local and central)	12.1.10.1	X	X	X	X	X	X	X	X	X	X
Serum Chemistries	12.1.10.2	X	X	X	X	X	X	X	X	X	X
Estimated Glomerular Filtration Rate (eGFR)	12.1.10.2	X									
PT, PTT, INR	12.1.10.2		X								X
ADA blood sample collection	14.2.8		X	X		X		X			X
JAK2 mutation burden blood sample collection	15.3	X									X
Inflammation markers	15.3		X				X				X
PK/PD Assessments											
PK blood samples PRE-dose only	12.1.13		X		X				X		X
PK blood samples PRE-dose and POST-dose	12.1.13						X[i]				
PD blood samples (serum iron, TSAT, transferrin, ferritin) PRE-dose only	12.1.13		X		X				X		X
PD blood samples (serum iron, TSAT, transferrin, ferritin) PRE-dose and POST-dose	12.1.13						X[i]				
Questionnaires (eDiary)											
Review eDiary/retraining	12.1.18		X	X	X	X	X	X	X	X	X
PROMIS® Fatigue Short Form 8a	12.1.18.1	X	X	X		X		X		X	X

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Table 6: Schedule of Assessments for Study PTG-300-11: Part 1a

Assessment	Reference to Section	Screening	Part 1a Double Blind[a]								
Study Week[b]		**Day -42 to -1**	**Wk 0 (Baseline)**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Wk 28**	**Wk 32[c]**
MFSAF v4.0	12.1.18.1	X[j]	Daily								
MPN-SAF TSS 10	12.1.18.1	X	X	X	X	X	X	X	X	X	X
PGI-S	12.1.18.1	X	X	X	X	X	X	X	X	X	X
PGI-C	12.1.18.1			X	X	X	X	X	X	X	X
EORTC QLQ-C30 (paper form)	12.1.19	X									X

ADA = anti-drug antibodies, CBC = complete blood count, ECG = electrocardiogram, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, HIPAA = Health Insurance Portability and Accountability Act, HIV = Human immunodeficiency virus, INR = International reference range, JAK2 = Janus kinase 2, MFSAF v4.0 = Myelofibrosis Symptom Assessment Form version 4.0, MPN-SAF TSS 10 = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score 10, PGI-C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PK = pharmacokinetic, PROMIS® = Patient-Reported Outcomes Measurement Information System, PT = Prothrombin time, PTT = Partial thromboplastin time, PV = polycythemia vera, TSAT = transferrin saturation.

[a] If a participant early terminates during Part 1a, complete the ET assessments as outlined in Table 8.

[b] Clinic visits after Week 0 (Baseline) and associated assessments during those visits should be conducted within an approximately 3-day window (±3 days). All study procedures should occur before study drug administration except as indicated (for example, post-dose PK/PD sample collection).

[c] **Week 32 visit is the end of Part 1a and beginning of Part 1b dosing. All participants will receive rusfertide starting Week 32 (See Section 12.2.3).**

[d] Participants enrolled at sites in the United States (US) must sign HIPAA authorization prior to the conduct of any study-specific procedures.

[e] See Section 12.2.1 regarding eDiary and participant contact during screening. After randomization, sites should contact participants 3 to 4 days prior to each clinic visit to remind them to complete eDiary entries and to bring their eDiary, and all used and unused study drug packages to the clinic.

[f] A complete dermatologic examination must be performed during screening. The window for complete dermatologic examination at Week 32 is ±6 weeks.

[g] ECG will be performed pre-dose, 2 to 8 hours post-dose, and 20 to 60 hours post-dose on the same day as pre/post dose PK/PD blood sample collection.

[h] For women of childbearing potential only.

[i] PK/PD blood sample collection: pre-dose on the day of study drug administration, and approximately 2 to 8 hours and 20 to 60 hours post dose.

[j] Reference Section 12.2.1 for multiple required collections during screening.

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Table 7: Schedule of Assessments for Study PTG-300-11: Part 1b

Assessment	Reference to Section	Part 1b[a] Open Label Treatment with Rusfertide[b]				
Study Weeks[c]		36	40	44	48	52
Administrative						
Participant contact reminder[d]	12.1.17	X	X	X	X	X
Study Drug Administration						
Dispense study drug kits	10.3	X	X	X	X	X
Administer study drug	10.3	Weekly				
Complete eDiary for dosing	12.1.18.2	Weekly				
Review eDiary for compliance/retraining	10.10, 12.1.18.2	X	X	X	X	X
Safety Assessments						
Full Physical Examination (including weight)	12.1.7					X
Complete Dermatologic Examination[e]	12.1.8					X
Problem-oriented Physical Examination (as needed)	12.1.7	As Needed				
Vital signs	12.1.5	X	X	X	X	X
12-lead ECG PRE-dose only	12.1.9	X				
12-lead ECG PRE-dose and POST-dose[f]	12.1.9					X
Spleen size	12.1.14					X
Adverse events	14.2	X	X	X	X	X
Concomitant medications	10.7, 10.8	X	X	X	X	X

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Table 7: Schedule of Assessments for Study PTG-300-11: Part 1b

Assessment	Reference to Section	Part 1b[a] Open Label Treatment with Rusfertide[b]				
Study Weeks[c]		36	40	44	48	52
Laboratory Assessments						
Urine pregnancy test[g]	12.1.12	X	X	X	X	X
Urinalysis	12.1.10.3	X	X	X	X	X
CBC (local and central)	12.1.10.1	X	X	X	X	X
Serum Chemistries	12.1.10.2	X	X	X	X	X
PT, PTT, INR	12.1.10.2					X
ADA blood sample collection	14.2.8		X			X
JAK2 mutation burden blood sample collection	15.3	X				X
Inflammation markers	15.3	X				X
PK/PD Assessments						
PK blood samples PRE-dose only	12.1.13	X	X			
PK blood samples PRE-dose and POST-dose[h]	12.1.13					X
PD blood samples (serum iron, TSAT, ferritin) pre-dose only	12.1.13	X	X			
PD blood samples (serum iron, TSAT, ferritin) pre-dose AND post-dose[h]	12.1.13					X
Questionnaires (eDiary)						
Review eDiary/retraining	12.1.18	X	X	X	X	X
PROMIS® Fatigue Short Form 8a	12.1.18.1	X	X	X	X	X

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Table 7: Schedule of Assessments for Study PTG-300-11: Part 1b

Assessment	Reference to Section	Part 1b[a] Open Label Treatment with Rusfertide[b]				
Study Weeks[c]		**36**	**40**	**44**	**48**	**52**
MFSAF v4.0	12.1.18.1	Daily				
MPN-SAF TSS 10	12.1.18.1	X	X	X	X	X
PGI-S	12.1.18.1	X	X	X	X	X
PGI-C	12.1.18.1	X	X	X	X	X

ADA = anti-drug antibodies, CBC = complete blood count, ECG = electrocardiogram, ET = Early Termination, INR = International reference range, JAK2 = Janus kinase 2, MFSAF v4.0 = Myelofibrosis Symptom Assessment Form version 4.0, MPN-SAF TSS 10 = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score 10, PD = pharmacodynamics, PGI-C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity PK = pharmacokinetic, PROMIS = Patient-Reported Outcomes Measurement Information System, PT = Prothrombin time, PTT = Partial thromboplastin time, TSAT = transferrin saturation.

[a] Part 1b begins once dosing has occurred with open label rusfertide at Week 32.

[b] If a participant early terminates during Part 1b, complete the ET assessments as outlined in Table 8.

[c] Clinic visits and associated assessments during those visits should be conducted within an approximately 3-day window (±3 days). All study procedures should preferably occur before study drug administration except as indicated (for example, post-dose PK/PD sample collection).

[d] Sites should contact participants 3 to 4 days prior to each clinic visit to remind them to complete eDiary entries and to bring their eDiary and all used and unused study drug packages to the clinic.

[e] The window for complete dermatologic examination at Week 52 is ±6 weeks.

[f] ECG will be performed pre-dose, 2 to 8 hours post-dose, and 20 to 60 hours post-dose on the same day as pre/post dose PK/PD blood sample collection.

[g] For women of childbearing potential only.

[h] PK/PD samples will be collected pre-dose on the day of rusfertide administration, and approximately 2 to 8 hours and 20 to 60 hours post dose.

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Table 8: Schedule of Assessments for Study PTG-300-11: Part 2

Assessment	Reference to Section	Part 2 Long-Term Extension																	ET	EOS/ Safety Follow-Up (4 Weeks Post Last Dose)[d]	New Cancer Events (6 & 12 Months Post Last Dose)
Study Weeks[a]		56	60	66[b]	72	78[b]	84	90[b]	96	102[b]	108	114[b]	120	126[b]	132	138[b]	144	150[b]	156[c]			
Administrative																						
Participant contact reminder[e]	12.1.17	X	X	X	X		X		X		X		X		X		X		X			
Study Drug Administration																						
Dispense study drug kits	10.3	X	X	X	X		X		X		X		X		X		X		X[f]			
Administer study drug	10.3	Weekly																	X[f]			
Complete eDiary for dosing	12.1.18.2	Weekly																				
Review eDiary for compliance/retraining	10.10, 12.1.18.2	X	X	X	X		X		X		X		X		X		X		X	X		
Safety Assessments																						
Full Physical Examination (including weight)	12.1.7						X				X				X				X	X		
Complete Dermatologic Examination[g]	12.1.8						X				X				X				X	X		
Problem-oriented Physical Examination (as needed)	12.1.7	As Needed																		X		
Vital signs	12.1.5	X	X	X	X		X		X		X		X		X		X		X	X	X	
12-lead ECG PRE-dose only	12.1.9		X		X		X		X				X		X		X		X	X		
12-lead ECG PRE-dose and POST-dose[h]	12.1.9										X											
Spleen size	12.1.14										X								X	X		
Adverse events	14.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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Table 8: Schedule of Assessments for Study PTG-300-11: Part 2

Assessment	Refer-ence to Section	Part 2 Long-Term Extension																		ET	EOS/ Safety Follow-Up (4 Weeks Post Last Dose)[d]	New Cancer Events (6 & 12 Months Post Last Dose)
Study Weeks[a]		56	60	66[b]	72	78[b]	84	90[b]	96	102[b]	108	114[b]	120	126[b]	132	138[b]	144	150[b]	156[c]			
Concomitant medications	10.7, 10.8	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Development of new cancer events[i]	12.2.7																					X
Laboratory Assessments																						
Serum pregnancy test[j]	12.1.12																		X	X		
Urine pregnancy test[j]	12.1.12	Every 4 weeks																			X	
Urinalysis	12.1.10.3		X		X		X		X		X		X		X		X		X	X	X	
CBC (local and central)	12.1.10.1	X	X	X	X		X		X		X		X		X		X		X	X	X	
CBC (local)[b]	12.1.10.1					X		X		X		X		X		X		X				
Serum Chemistries	12.1.10.2	X	X	X	X		X		X		X		X		X		X		X	X	X	
PT, PTT, INR	12.1.10.2		X						X						X				X	X		
ADA blood sample collection	14.2.8		X		X				X		X				X		X		X	X	X	
JAK2 mutation burden blood sample collection	15.3		X						X						X				X	X		
Inflammation markers	15.3		X		X				X		X				X		X		X	X	X	
PK/PD Assessments																						
PK blood samples PRE-dose only	12.1.13		X		X		X		X				X		X		X		X	X	X	
PK blood samples PRE-dose and POST-dose[k]	12.1.13										X											

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Table 8: Schedule of Assessments for Study PTG-300-11: Part 2

Assessment	Reference to Section	Part 2 Long-Term Extension																	ET	EOS/ Safety Follow-Up (4 Weeks Post Last Dose)[d]	New Cancer Events (6 & 12 Months Post Last Dose)
Study Weeks[a]		56	60	66[b]	72	78[b]	84	90[b]	96	102[b]	108	114[b]	120	126[b]	132	138[b]	144	150[b]	156[c]			
PD blood samples (serum iron, TSAT, ferritin) pre-dose only	12.1.13		X		X		X		X				X		X		X		X	X	X	
PD blood samples (serum iron, TSAT, ferritin) pre-dose AND post-dose[k]	12.1.13										X											
Questionnaires (eDiary)																						
Review eDiary/retraining	12.1.18	X	X	X	X		X		X		X		X		X		X		X	X	X	
PROMIS® Fatigue Short Form 8a	12.1.18.1	X	X	X	X		X		X		X		X		X		X		X	X	X	
MFSAF v4.0	12.1.18.1	Daily																				
MPN-SAF TSS 10	12.1.18.1	X	X	X	X		X		X		X		X		X		X		X	X	X	
PGI-S	12.1.18.1	X	X	X	X		X		X		X		X		X		X		X	X	X	
PGI-C	12.1.18.1	X	X	X	X		X		X		X		X		X		X		X	X	X	

ADA = anti-drug antibodies, CBC = complete blood count, ECG = electrocardiogram, EOS = end of study, ET = Early Termination, INR = International reference range, JAK2 = Janus kinase 2, MFSAF v4.0 = Myelofibrosis Symptom Assessment Form version 4.0, MPN-SAF TSS 10 = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score 10, PD = pharmacodynamics, PGI-C = Patient Global Impression of Change, PGI-S = Patient Global Impression of Severity, PK = pharmacokinetic, PROMIS = Patient-Reported Outcomes Measurement Information System, PT = Prothrombin time, PTT = Partial thromboplastin time, TSAT = transferrin saturation.

[a] Clinic visits and associated assessments during those visits should be conducted within an approximately 3-day window (±3 days). All study procedures should preferably occur before study drug administration except as indicated (for example, post-dose PK/PD sample collection, ECG).

[b] Optional visits. If the participant's hematocrit is not stable at the scheduled visits, consider checking a local CBC (only) at these visits and adjust dose if necessary.

[c] Week 156 is the end of Part 2 and the start of Part 3. For participants who complete Part 2 and do not continue to Part 3, the Week 156 visit is also considered the end of treatment (EOT) visit. These participants will also have an EOS/Safety Follow-Up visit performed. Participants must provide consent to continue into Part 3.

[d] Follow-up procedures are to occur 4 weeks after last dose whether the participant completes the study or terminates early. Adverse event assessment includes assessment for new cancers.

[e] Sites should contact participants 3 to 4 days prior to each clinic visit to remind them to bring their eDiary and all used and unused study drug packages to the clinic.

[f] Dispense drug to participants continuing onto Part 3.

[g] The window for complete dermatologic examination at Weeks 84, 108, 132, 156, and ET is ±6 weeks.

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Table 8: Schedule of Assessments for Study PTG-300-11: Part 2

Assessment		Part 2 Long-Term Extension																				
Study Weeks[a]	Refer-ence to Section	56	60	66[b]	72	78[b]	84	90[b]	96	102[b]	108	114[b]	120	126[b]	132	138[b]	144	150[b]	156[c]	ET	EOS/ Safety Follow-Up (4 Weeks Post Last Dose)[d]	New Cancer Events (6 & 12 Months Post Last Dose)

[h] ECG will be performed pre-dose, 2 to 8 hours post-dose, and 20 to 60 hours post-dose on the same day as pre/post dose PK/PD blood sample collection.
[i] Contact participants approximately 6 and 12 months after the last dose to assess new cancer events for participants who permanently discontinue rusfertide at or before Week 156.
[j] For women of childbearing potential only. Every-4-weeks home urine pregnancy tests will be provided and used for months when participants are not scheduled to visit the clinic.
[k] PK/PD samples will be collected pre-dose on the day of rusfertide administration, and approximately 2 to 8 hours and 20 to 60 hours post dose.

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Table 9: Schedule of Assessments for Study PTG-300-11: Part 3

Assessment		Part 3 Rusfertide Treatment Extension	
Study Weeks[a]	**Reference to Section**	**Week 168, Week 180, Week 192, Week 204, etc., and Every 12 Weeks Until EOS Part 3**	**EOS Part 3**[b]
Dispense study drug kits	10.3	X	
Problem-oriented Physical Examination (including weight)[c]	12.1.7	X	X
Complete Dermatologic Examination[d]	12.1.8	X	X
Vital signs	12.1.5	X	X
Adverse events	14.2	X	X
Concomitant medications	10.7, 10.8	X	X
Urine pregnancy test[f]	12.1.12	X	X
CBC (local)	12.1.10.1	X	X
Serum chemistries (local)	12.1.10.2	X	X

Note: Week 156 is the start of Part 3.
CBC = complete blood count, EOS = end of study

[a] Clinic visits and associated assessments during those visits should be conducted within an approximately 2-week window. All study procedures should preferably occur before study drug administration.

[b] The EOS visit should be performed after the participant permanently discontinues rusfertide and/or study participation.

[c] At EOS Part 3, participants should undergo a full physical examination (including weight).

[d] Dermatologic examination required every 24 weeks. The window for complete dermatologic examination is ±12 weeks. If a dermatologic examination was completed within 12 weeks of EOS, it does not need to be repeated.

[f] For women of childbearing potential only. Pregnancy testing should be performed every 4 weeks ±7 days. Home urine pregnancy tests will be provided and used when participants are not scheduled to visit the clinic.

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12.1. Procedural Details

12.1.1. Informed Consent

Participants or their legal guardian must give written informed consent using a properly executed written ICF before any study-specific procedures are performed. The protocol's risks, potential benefits, and procedures, and the participant's obligations should be explained in detail. The participant and/or guardian should be given time to review the consent document and all questions should be answered. The informed consent process should be documented in the participant's medical record and the investigator must provide a copy of the signed ICF to each participant.

Depending on local Competent Authority requirements, additional consent documents may be required, such as Health Insurance Portability and Accountability Act HIPPA in the United States.

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12.1.2. Demographic/Medical History/Family Cancer History

Demographic characteristics are age, sex, race, ethnicity.

Medical history should include all clinically significant medical conditions both past and present, hospitalizations, surgeries, and thrombotic events. Performing a review of systems to identify relevant medical history is recommended.

The family cancer history, including MPNs, should be collected for the first degree relatives.

12.1.3. PV History

PV history that will be collected include but are not limited to:

- Date of PV diagnosis
- Participants must meet 2016 WHO criteria for PV. These criteria include a bone marrow biopsy. A historic biopsy is acceptable if the biopsy report is available.
- Prior and current therapy for PV
  - All available information including dosing regimen of cytoreductive therapies, start/stop dates for 1 year and therapies received for prior years.
- History of phlebotomies for at least 6 months prior to randomization and preferably for 1 year before randomization.
- Hematocrit values for at least 6 months prior to randomization and preferably for 1 year before randomization.
- Complications of PV including thrombotic, cardiovascular, and cerebrovascular events
- Assessment of whether the participant has symptoms of splenomegaly (Section 14.7).

- For participants who underwent erythrocytapheresis prior to screening each procedure will be counted as one phlebotomy and should be reported as a phlebotomy. Note that erythrocytapheresis is not allowed after the participant begins screening.

12.1.4. Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be assessed at screening. ECOG performance is measured on a 6-point scale:

- 0 = Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction);
- 1 = Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work);
- 2 = Symptomatic, < 50% in bed during the day (Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours);
- 3 = Symptomatic, > 50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours);
- 4 = Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) and
- 5 = Dead.

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12.1.5. Vital Signs

Vital signs (temperature, pulse, respirations and blood pressure) will be measured at the times shown in Table 6, Table 7, Table 8, and Table 9. Vital signs should be measured after the participant has been sitting or lying quietly for 5 minutes.

12.1.6. Weight and Height

Weight and height will be measured at the indicated visits and the results reported in centimeters (cm) or kilograms (kg), respectively. Weight is included in the full physical examination.

12.1.7. Physical Examinations

Full physical examinations should include weight and examination of the head, neck, chest/lungs, cardiovascular (heart and peripheral arteries), abdomen including spleen size, and extremities. Neurologic examination and examination of the genitourinary system should be performed in participants with relevant history or symptoms. Other body systems should be examined as appropriate.

Full examinations at screening must include assessment of encephalopathy and ascites.

Problem-oriented physical examinations should be performed as needed to evaluate adverse events. The problem-oriented physical examination should focus on organ systems affected by the adverse event.

12.1.8. Dermatological Examinations

12.1.8.1. Screening Examination

A complete dermatological examination that evaluates all sun-exposed parts of the body must be performed during screening period (up to 4 weeks) to determine study eligibility.

It is preferable but not required that a dermatologist perform the dermatological examination during screening. If a dermatologist is not available for the screening examination, the investigator or other medical personnel who are trained to perform skin examinations must perform the screening examination. See Section 12.1.8.2 if a dermatologist did not perform the screening examination.

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12.1.8.2. Post-Randomization Examination

- Within 10 weeks after randomization: If a dermatologist did not perform the examination during the screening period, it is strongly encouraged that a dermatologist performs a complete skin examination within 10 weeks after randomization. New lesions identified during a dermatologist's examination performed after randomization will be treated as adverse events and will not affect study eligibility. New lesions identified by the dermatologist, particularly cancers, should be followed according to local standard of care.
- Examinations at Scheduled Visits: It is preferable but not required that a dermatologist perform the dermatological examination at subsequent scheduled visits. To facilitate examinations by dermatologists at scheduled visits after randomization, the window is ±6 weeks.

12.1.9. Electrocardiogram (ECG)

A standard 12-lead ECG will be performed after the participant has been resting quietly, lying down for at least 5 minutes. The ECG should be performed on the day of dosing before administration of study drug unless otherwise specified in the schedule of assessments.

The investigator will document interpretation of each ECG. Any text printed by the cardiograph's automated algorithm will be considered confirmed by the investigator if not crossed out. The ECGs will be classified as being in one of 3 categories: normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). Each abnormal finding will be separately documented as either NCS or CS, along with a description of the abnormal finding.

In addition to the investigator's classification of each ECG overall, the ECG parameters of ventricular rate, PR interval, RR interval, rhythm assessments, QRS duration, QT interval

(uncorrected), and QTcF interval (QT interval corrected for heart rate according to Fridericia's formula) will be recorded in the eCRF. All new CS findings will be reported as AEs.

12.1.10. Laboratory Assessments

Laboratory tests will be performed at the time points specified in the Schedule of assessments (Table 6, Table 7, Table 8, and Table 9). The specific tests to be performed are listed in Appendix 3.

The Laboratory manual should be referenced for handling of all Central Laboratory collections.

12.1.10.1. Hematology

For Parts 1a, 1b, and 2, both local laboratories and the Central Laboratory will perform complete blood counts. Reticulocytes will be performed at Central Laboratory only (Appendix 3). For Part 3, CBC (including reticulocytes) will be conducted by the local laboratory at each site.

The local hematology results will be used for eligibility, for adjusting the dose of study drug and for study endpoints as appropriate. At scheduled assessments, hematology assessments must be performed before the participant is dosed to determine if a change in dose is required.

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12.1.10.2. Blood Chemistry and Coagulation Testing

For Parts 1a, 1b, and 2, the Central Laboratory will perform routine safety blood chemistry assessments (Appendix 3). Estimated GFR will be performed using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. The Central Laboratory will also perform coagulation tests (PT, PTT and INR) (Appendix 3).

For Part 3, safety blood chemistry assessments will be conducted by the local laboratory at each site.

12.1.10.3. Urinalysis

The Central Laboratory will perform all routine urinalyses. A dipstick assessment will be performed and if the dipstick shows abnormalities, then microscopy will be performed.

12.1.11. Virus Serology

Hepatitis B surface antigen (HBsAG), hepatitis B core antibody (HBc), hepatitis C antibody (HCAb), and human immunodeficiency virus (HIV) antibody testing will be performed.

Participants who are negative for HBsAG and positive for HBc will have HBV DNA testing.

Participants positive for Hepatitis C will have hepatitis C RNA testing.

Participants who are Hepatitis B positive or Hepatitis C positive are eligible.

Participants who are HIV positive are eligible if their HIV infection is controlled.

12.1.12. Pregnancy Testing

Women of childbearing potential will be tested routinely for pregnancy. A serum test for human chorionic gonadotropin (HCG) will be performed during screening and at EOT/ET. A urine test for pregnancy will be performed at scheduled visits during treatment with study drug (Table 6, Table 7, Table 8, and Table 9). A urine home pregnancy test will be performed every 4 weeks for months when visits are not scheduled. Sites should contact the participant to remind her to do the pregnancy test and to obtain the results every 4 weeks. Urine pregnancy tests are not required at unscheduled or optional visits. A positive urine pregnancy test should be confirmed with a serum test as soon as possible. Study drug must not be administered to a woman who is pregnant or lactating.

12.1.13. Pharmacokinetics and Pharmacodynamics

Pharmacodynamic markers are serum iron, TSAT, transferrin, and ferritin.

Blood will be collected for pre-dose rusfertide levels and for pre-dose changes in serum iron, TSAT, ferritin, and transferrin at the time points indicated in the Schedule of assessments (Table 6, Table 7, and Table 8). In addition, blood will be collected for PK and PD pre-dose, and should be collected 2 to 8 hours post-dose and 20 to 60 hours post-dose in Week 16, Week 52 and Week 108.

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12.1.14. Spleen Size

Spleen size should be assessed at the indicated time points by MRI, ultrasound, or CT scan (in countries where CT is approved). MRI is the preferred procedure. The same technique should be used for baseline and follow-up assessments. Baseline assessment must be performed before randomization. For post-randomization assessments of spleen size, the window for performing follow-up assessments is ±4 weeks. The maximum spleen length should be reported in centimeters.

In addition to radiographic measurements, spleen size may be assessed by physical examination and reported as centimeters below the left costal margin.

12.1.15. Incidental Findings

Any lesion or mass detected by physical examination or imaging during screening that is suspicious for malignancy should be evaluated further. Participants should be enrolled only if these lesions have been assessed to be not malignant. For example, any incidental intra-abdominal mass/masses discovered during baseline radiological spleen assessments, with or without any related sign or symptom, should be further evaluated to rule out malignancy before randomization.

12.1.16. Bone Marrow Biopsy

A bone marrow biopsy should be performed as part of standard-of-care in participants who develop evidence for leukemic transformation or post-PV myelofibrosis.

12.1.17. Participant Contact Reminder

At screening contact participant 7 days prior to randomization to remind the participant to complete the PGI-S and MFSAF v4.0 patient reported outcomes. In order to be eligible, a participant must complete at least 4 MFSAF v4.0 assessments in the week before randomization.

Before each scheduled visit remind participant to complete the MFSAF v4.0 daily assessments and to bring the eDiary and study drug supplies to the clinic.

12.1.18. eDiary

An eDiary device will be used for recording dosing and five of the patient reported outcomes. The participant will be trained on using the eDiary. Participant should complete the eDiary at home or in the clinic at the scheduled times for dosing and PROs. In Part 3, participants are not required to complete eDiaries.

The participant should bring the eDiary to each clinic visit. Study staff should review eDiary entries for completeness and, if necessary, retrain the participant on the use of the eDiary.

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12.1.18.1. Patient Reported Outcomes (eDiary)

Five Patient Reported Outcomes (PROs) are collected in the study using the eDiary.

The following PRO must be completed via the eDiary every day:

- MFSAF v4.0

  The seven questions assessing myelofibrosis symptoms will be completed by the participants every day to evaluate his/her symptoms over the past 24 hours once the diary is dispensed. The participant will select ranking (absence [0] to worst imaginable [10] to assess fatigue, night sweats, itching, abdominal discomfort, pan under ribs, feeling of fulness and bone pain in the eDiary.

The following PROs will be completed at scheduled visits using the eDiary:

- PROMIS Fatigue Short Form 8a (PROMIS):

  The PROMIS Fatigue Short Form 8a contains 8 questions relating to fatigue experienced by the participant in the 7 days prior to completing the form. The form will be completed at the following times:

  – Once between Day -42 and Day -7 (inclusive)

  – On site on Day 1 Week 0 before dosing with study drug

  – On site prior to dosing at visits specified in the schedules of assessments (Table 6, Table 7, and Table 8).

- MPN-SAF TSS 10:

The 10 questions assessing symptoms using MPN-SAF TSS 10 will be completed by the participants. The participant will select ranking (absence [0] to worst imaginable [10]) to assess fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, itching, bone pain, fever, and unintentional weight loss. The questionnaire should be completed prior to dosing. The form will be completed at the following times:

- Once between Day -42 and Day -7 (inclusive)
- On site on Day 1 Week 0 before dosing with study drug
- On site prior to dosing at visits specified in the schedules of assessments (Table 6, Table 7, and Table 8).

- PGI-S:

  This is a single question to assess the severity of the PV symptoms during 24 hours prior to dosing. The participant will select ranking using a scale from "none" (0) to "severe" (3). This scale is less likely to be impacted to recall error. The participant will complete this assessment in the eDiary starting at the following time points:

  - Once between Day -42 and Day -7 (inclusive)
  - On site on Day 1 Week 0 before dosing with study drug
  - On site prior to dosing at visits specified in the schedules of assessments (Table 6, Table 7, and Table 8).

- PGI-C:

  The participant will independently rate his/her overall impression of the change in their PV condition since randomization. This form will be completed prior to dosing during the site visit at visits specified in the schedule of assessments.

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12.1.18.2. Study Drug Administration

The eDiary will be used to collect all study drug administration information including date/time of administration, kit number and kit dose strength.

The diaries should be completed on the day study drug is administered. Participants should bring the eDiary to the clinic at each visit for review by the staff.

12.1.19. Paper Form EORTC QLQ-C30

The participant will independently rate his/her overall impression of the impact of treatment on the participant's quality of life using the EORTC QLQ-C30. The questionnaire will be provided in paper form and will be completed during screening for a baseline assessment and at Week 32 after the eDiary has been completed and prior to dispensing drug for Part 1b.

12.2. Specific Visit Information

12.2.1. Screening

The screening period is 42 days (Day -42 to Day -1) and begins once the participant signs written informed consent (and HIPAA authorization for US participants only) to participate in this study before undergoing any study-specific procedures. Upon signing the ICF, each participant should be registered in the IxRS to receive a Participant ID for the duration of participation in the study.

Screen Failures

Participants who sign an informed consent but fail to be randomized for any reason will be considered a screen failure. The screen failure reason will be collected.

Rescreening

Participants who are screen failures may undergo repeat screening once (a total of 2 screenings) and the initial Participant ID will be retained. Before repeat screening begins, the participants must reconsent to participate in the trial.

All screening assessments must be repeated at rescreening with the exception of radiographic assessment. Radiographic assessment of spleen size does not need to be repeated if the participant is randomized within 8 weeks of the day of the procedure. Dermatologic examinations must be repeated during the rescreening period. Any findings from a dermatologic examination performed by a dermatologist during initial screening should be reported as medical history.

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CBC and Clinical Laboratory Assessments

Local laboratory CBC results are used for eligibility. The central lab results are used for all other eligibility tests. Participants with laboratory test results that do not meet study eligibility requirements may undergo repeat testing during the 42-day screening period.

Participants must meet eligibility criteria for hematocrit (<45%), WBC (4000/µL to 20,000/µL inclusive) and platelets (100,000/µL to 1,000,000/µL inclusive) in a CBC performed at the site's local laboratory within one day prior to randomization (Day 1).

Phlebotomies During Screening

Participants with initial screening hematocrit ≥45% should undergo one or more phlebotomies during the screening period in order to bring the hematocrit value below 45%. Additionally, investigators may perform phlebotomies in participants with initial screening hematocrit slightly lower than 45% to ensure hematocrit is <45% at randomization. Phlebotomies performed within an 8-day period will be counted as a single phlebotomy.

NOTE: Phlebotomy is not allowed within 6 days prior to randomization.

Polycythemia Vera History

Participants must meet WHO Criteria for PV (Appendix 1). The participant's PV history including phlebotomies, hematocrit and all available information for cytoreductive therapies for at least 1 year before screening should be available unless the participant was diagnosed with PV less than 1 year before screening.

Cytoreductive therapy history should include all agents received, start/end dates (partial dates are acceptable) when each agent was administered and doses if available. Participants must be on a stable dose of cytoreductive therapy (or not be receiving cytoreductive therapy for the following time periods before randomization (i) hydroxyurea 2 months; (ii) ruxolitinib 2 months; and (iii) interferon 6 months.

Spleen Size and Symptoms of Splenomegaly

Spleen size should be assessed at the indicated time points by MRI, ultrasound, or CT scan (in countries where CT is approved). MRI is the preferred procedure. Complete physical examinations should incorporate splenic assessments.

All participants should be queried for symptoms of splenomegaly. Symptomatic splenomegaly includes fatigue, night sweats, itching, abdominal discomfort, pain under the left ribs, feeling of fullness after eating and bone pain. Investigators should assess carefully whether such symptoms are due to splenomegaly or to other conditions and document their assessment.

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Cancer Screening Counseling

Participants should be counseled to undergo routine cancer screening according to guidelines for the participant's age, sex, and risk factors.

Risk reduction counseling involves advising participants to follow standard guidance for reducing the risk of developing cancer, such as reducing sun exposure, using high protection sunscreen, not smoking, limiting alcohol consumption, and eating a healthy diet.

eDiary

An eDiary will be used for recording dosing and five PROs. The participant should be trained on the use of the eDiary on the first day of screening.

During screening participants should complete the eDiary as follows:

- PROMIS Fatigue Short Form 8a: Once between Day -42 and Day -7 (inclusive)
- MFSAF v4.0: Daily starting on the first day of screening
- MPN-SAF TSS 10: Once between Day -42 and Day -7 (inclusive)
- PGI-S: Once between Day -42 and Day -7 (inclusive).

NOTE: Participants who do not complete at least 4 days of MFSAF v4.0 in the week prior to randomization are not eligible for enrollment. Contact the participant 7 days before randomization to ensure completion of the MFSAF v4.0.

The investigator should exercise discretion in enrolling participants who demonstrate difficulty with completing the MFSAF v4.0 daily diary.

EORTC QLQ-C30

The EORTC QLQ-C30 will be provided in paper form. The participant must complete the questionnaire once. This may be completed at any clinic visit during screening.

12.2.2. Randomization: Day 1 of Week 0 - First Dose

- Eligibility must be confirmed prior to randomization.
  - Hematocrit (<45%), WBC (4000/μL to 20,000/μL inclusive) and platelets (100,000/μL to 1,000,000/μL inclusive) in a CBC performed at the site's local laboratory within one day prior to randomization (Day 1).
  - At least 4 days of MFSAF v4.0 assessments within 1 week prior to randomization including assessment on day of randomization.
- MPN-SAF TSS 10, PGI-S and PROMIS before randomization.
- If necessary, re-training on use of the eDiary should be provided.
- Randomize the participant using IxRS.
- Study drug administration
  - The first dose of study drug must be administered on the day of randomization.
  - The starting dose of rusfertide/placebo is 19 mg by subcutaneous injection once a week. The participant or care giver should be instructed on administration of study drug.
  - The participant should be instructed on completion of the eDiary entries for study drug administration.

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12.2.3. End of Part 1a (Week 32)/Beginning of Part 1b

All participants who complete 32 weeks of treatment in Part 1a will be eligible to continue in Part 1b and receive open label rusfertide. Since participant randomized to placebo group in Part 1a will receive 19 mg of active drug, the site and participant will potentially be unblinded to treatment in Part 1a. Because of potential unblinding at the start of Part 1b, **all required assessments at Week 32 must be completed prior to initiating dosing in Part 1b**.

Before accessing IxRS to dispense study drug for Part 1b, the investigator or participant must complete all Week 32 assessments including:

- Review eDiary for dosing and MFSAF v4.0 for completeness
- PROMIS Short Form 8a, MFSAF v4.0, PGI-C, PGI-S, MPN-SAF TSS 10 (eDiary)
- EORTC QLQ-C30 (paper form)

- AEs and concomitant medications.

12.2.4. End of Part 1b (Week 52)/Beginning of Part 2

Participants who complete Part 1b will enter Part 2 of this study. The duration of dosing in Part 2 is 104 weeks.

Required and Optional Visits

Part 2 has required visits and optional visits as described in Table 8. The first two visits in Part 2 will be 4 weeks apart. Afterwards, clinic visits will be every 12 weeks, with optional visits every 6 weeks if the visits are required for possible dose adjustment. The investigator should use an optional visit if the participant's hematocrit results in a required visit suggest that the participant may require further dose adjustment or hematocrit monitoring before the next required visit. At the optional visit the only required assessment is a local CBC. Investigators may perform additional assessments if deemed necessary by the investigator.

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12.2.5. End of Part 2 (Week 156)/Beginning of Part 3

Participants who complete Part 2 and, in the opinion of the investigator, are continuing to derive benefit from rusfertide may be eligible to enroll in Part 3. Study drug will be dispensed at Week 156 for participants continuing on to Part 3 if appropriate. The next scheduled visit for participants in Part 3 is Week 168 (see Table 9).

12.2.5.1. End of Study/Safety Follow-Up Visit for Participants Discontinuing at or Before Week 156

For participants discontinuing at or before Week 156, see Table 8 for EOS assessments, and the safety follow-up period.

12.2.6. Part 3 to End of Study

In Part 3, visit frequency is every 12 weeks (±2 weeks) until the EOS visit (see Table 9 for details). All study procedures should be performed prior to study drug administration.

12.2.7. Early Termination

In the event that any participant discontinues before completing Part 2 of the study, regardless of reason, reasonable efforts should be made to have the participant return for an early termination visit and have the End of Treatment evaluations (Table 8, ET column). The date the participant discontinued the study drug and the specific reason for discontinuation will be recorded in the eCRF. This will include reasons such as discontinued due to disease progression, lack of efficacy, or withdrawn due to Adverse Event. This information will be used to summarize the reasons for study withdrawal.

Participants who permanently discontinue rusfertide at or before Week 156 and do not enter Part 3 will be contacted (for example, by telephone) approximately 6 and 12 months after their last dose to assess the occurrence of any new cancer events. Participants who enter Part 3 will have

safety events collected through the EOS Part 3 visit, with no additional protocol-required postdose contacts after EOS Part 3.

12.2.7.1. Follow-Up for Withdrawal for AEs

Participants who stop study drug for an AE or an SAE should be followed closely until the event has resolved or stabilized, until the event is otherwise explained, or until the participant dies or is lost to follow-up. For AEs and SAEs that require prolonged treatment (for example, a new cancer) the event should be followed until treatment has begun. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

12.2.7.2. Participant Replacement Policy

Participants who withdraw from the study prior to completion of the study will not be replaced.

12.2.8. Unscheduled Visits

Investigators may perform an unscheduled visit for any reason. The investigator should perform assessments deemed important by the investigator. Specific laboratory kits and case report forms will be provided for unscheduled visits.

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13. ASSESSMENT OF EFFICACY

13.1. Clinical Endpoints

13.1.1. Hematocrit

Hematocrit is a standard clinical laboratory test to assess erythropoiesis. Hematocrit will be monitored to assess phlebotomy requirement as noted above. Blood samples for hematocrit will be collected during scheduled study visits.

13.1.2. Phlebotomy

Intermittent phlebotomy to maintain hematocrit lower than 45% is standard of care for patients with PV.

13.2. Patient Reported Outcomes (PROs)

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13.2.1. PROMIS Fatigue Short Form 8a

The Patient Reported Outcomes Measurement Information System (PROMIS) Short Form 8a (Appendix 7) is an NIH-developed fatigue survey. The 8-item instrument asks the patient about fatigue experience and impact over the past 7 days.

13.2.2. Myelofibrosis Symptom Assessment Form Version 4.0 (MFSAF v4.0)

The Myelofibrosis Symptom Assessment Form version 4.0 (MFSAF v4.0) (Appendix 5) is a questionnaire developed by the Patient-Reported Outcome (PRO) Consortium's Myelofibrosis Working Group that focuses on the seven core symptoms of myelofibrosis: fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain (Gwaltney 2017). The MFSAF v4.0 asks participants to report symptom severity at its worst for each of the seven items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale.

13.2.3. Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score 10 (MPN-SAF TSS 10)

The MPN-SAF TSS 10 (Appendix 6) is a 10-item questionnaire measurement tool for symptoms of myeloproliferative neoplasms (MPNs). The MPN-SAF is a reliable instrument that has been validated for evaluating symptoms associated with PV (Emanuel 2012).

13.2.4. Patient Global Impression of Severity (PGI-S)

The Patient Global Impression of Severity (PGI-S) is a single question to assess how the severity of PV symptoms over the last 24 hours prior to dosing (Appendix 8). The patient will determine the severity of their PV symptoms on a 4-point scale ranging from "None" (0) to "Severe" (3) at the time of the assessment.

13.2.5. Patient Global Impression of Change (PGI-C)

The Patient Global Impression of Change (PGI-C) (Appendix 9) is a simple, commonly used instrument to obtain a participant's overall assessment of the impact of treatment on the participant's quality of life. A participant will compare his/her condition from the start of the study on a 5-point scale ranging from "Much better" (1) to "Much worse" (5) at the time of the assessment.

13.2.6. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) (Appendix 10) is a commonly used, validated instrument to obtain a participant's overall assessment of the impact of treatment on the participant's quality of life. The EORTC QLQ-C30 consists of 5 functional scales (physical, role, cognitive, emotional, and social functioning), a global quality of life (QoL) scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (appetite loss, diarrhea, dyspnea, constipation, insomnia, financial impact). For the functional and the global QoL scales, a higher score indicates better health. For the symptom scales, a higher score indicates more symptom burden. The QLQ-C30 summary score is calculated as the mean of the combined 13 QLQ-C30 scale and item scores (excluding global QoL and financial impact), with a higher score indicating a better health-related QoL.

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14. ASSESSMENT OF SAFETY

14.1. Safety Parameters

Safety will be assessed by the following parameters:

- Adverse events and concomitant medications will be evaluated throughout the course of the study.
- Clinical safety laboratory tests, physical examination, vital signs (heart rate, temperature, systolic and diastolic blood pressure, respiratory rate) and 12-lead ECG findings will be assessed.

14.2. AEs

In this study, AEs and SAEs will be reported in all participants from the time the participant signs the ICF until the completion of the end of study visit, with the exception of cancer events and thromboembolic events identified during screening. All cancer events and thromboembolic events identified between signing the ICF and prior to randomization must be reported as medical history on the Medical History CRF and not as adverse events on the AE CRF. Reporting these events as medical history facilitates proper evaluation of treatment-emergent cancers and thromboembolic events.

Treatment-emergent AEs and SAEs will be evaluated from study drug dosing until the end of study/safety follow-up visit performed 4 weeks after the last dose of study drug.

Participants who permanently discontinue rusfertide at or before Week 156 and do not enter Part 3 will be contacted (for example, by telephone) approximately 6 and 12 months after their last dose to assess the occurrence of any new cancer events. Participants who enter Part 3 will have safety events collected through the EOS Part 3 visit, with no additional protocol-required postdose contacts after EOS Part 3.

14.2.1. Definition of AE

An AE is any event, side effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE may include an increase in severity of a pre-existing condition included in a participant's medical history, and symptoms or clinical sequelae of a suspected overdose. "Lack of efficacy" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

The investigator should attempt to establish a diagnosis of the event based on the signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE (and SAE if serious) and not the individual signs/symptoms.

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14.2.2. Severity of an AE

Severity of AEs will be assessed and reported following Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 criteria. Severity of AEs that do not match CTCAE criteria will be assessed as follows:

- **Mild (Grade 1):** awareness of sign or symptom but easily tolerated
- **Moderate (Grade 2):** discomfort enough to cause interference with usual activity
- **Severe (Grade 3):** incapacitating with inability to work or do usual activity
- **Life-threatening (Grade 4):** could reasonably lead to death without medical intervention
- **Fatal (Grade 5)**

14.2.2.1. Relationship of an AE to Study Drug

The investigator will assess the relationship between study drug and the occurrence of each AE. The investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and the CRF. Alternative causes, such as medical history, concomitant

therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not Related:** The event is clearly related to other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the study drug.
- **Unlikely:** The event was most likely produced by other factors such as the participant's clinical state, therapeutic interventions, or a concomitant drug administered to the participant and does not follow a known response to the study drug.
- **Possibly:** The event follows a reasonable temporal sequence from the time of study drug administration or follows a known response to the study drug but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Related**: The temporal relationship is compelling between the administration of the study drug and the AE cannot be explained by the participant's medical condition or other therapies.

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14.2.2.2. Action Taken with Study Medications

Action taken with study medications will be recorded on the AE CRF page, as follows, regardless if a particular category is possible or not in this study:

- Dose Increased
- Dose Not Changed
- Dose Reduced
- Dose Delayed
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Unknown

14.2.2.3. Outcome of an AE

Outcome of an AE will be recorded on the AE CRF as follows:

- Recovered/Resolved
- Recovering/Resolving

- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolved
- Fatal
- Unknown

14.2.3. Definition of Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

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Important medical events that are not one of the above may be considered to be SAEs by the investigator when, based upon appropriate medical judgment, they are considered to be clinically significant and may jeopardize the participant, or when medical or surgical intervention may be required to prevent one of the outcomes listed above.

An AE is considered "life-threatening" if, in the opinion of either the investigator or the sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other seriousness criteria to determine whether they quality as an SAE.

Preplanned hospitalizations (for example, elective procedures for preexisting conditions that did not worsen) are excluded from SAE reporting. However, if during the pre-planned hospitalization, an event occurs which prolongs the hospitalization or meets any other serious criteria, that event will be considered as an SAE.

Hospitalizations for administrative purposes (for example, to perform a scan or for blood transfusion) are not considered to be SAEs unless the condition requiring the administrative hospitalization meets other criteria for being serious.

Note that death is an outcome of an AE and not an AE in itself. The event that was the proximate cause of death should be reported as an AE.

Disease progression will not be considered as an SAE. The events leading to disease progression if assessed as serious by the investigator should be collected as an SAE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria under Section 14.2.3. An AE of severe intensity may not be considered serious.

14.2.4. Definition of Adverse Events of Special Interest (AESI)

An AESI (serious or nonserious) is one of scientific and medical concern for which there is a specific clinical interest in connection with the study treatment, and that requires ongoing monitoring and rapid communication by the investigator to the sponsor. Such event might warrant further investigation in order to characterize and understand it. AESIs are to be defined by the Clinical Team with regular updates as necessary and described in the SAP. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (for example, regulators) might also be warranted.

14.2.5. Pregnancy

The investigator must report to the sponsor any pregnancy occurring in a study participant (or participant's partner) during the participant's participation. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE unless the birth results in a congenital anomaly/birth defect or the woman experiences an SAE (for example, hospitalization for preeclampsia). Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as an AE or SAE.

If the participant is female and becomes pregnant while in the study, the participant will be promptly withdrawn from the study.

A pregnancy should be followed-up until reporting of the pregnancy's outcome and the birth date.

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14.2.6. Abuse, Misuse, Overdose and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure using a separate paper-based (Special Situation Report Form) whether or not they result in an AE/SAE as described in sections 14.2.1. and 14.2.3.. If special situation results in an SAE, the SAE should be reported.

Individuals who identify a potential special situation should immediately report this via the Special Situation Report Form within 7 calendar days to the contact information provided in the site manual.

The special situation report (SSR) is defined as any of the following events:

- Abuse: persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- Misuse: situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or indication(s) or within the legal status of its supply

- Medication Error: an unintentional error in the drug treatment process (prescribing, dispensing or administration, including incorrect dose or poor-quality administration) of a medicinal product while in the control of trial site staff or a participant that leads to harm or has the potential to lead to harm.
- Overdose: the administration of a quantity of medicinal product given per administration or per day, which is above the maximal recommended dose according to the protocol.

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors. The administration and/or use of an expired investigational product should be considered as a reportable medication error.

14.2.7. Product Complaints

A product complaint is a verbal written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Product complaints could include suspicion that a trial intervention has been counterfeited.

Individuals who identify a potential product complaint situation should immediately report this to the sponsor as outlined in the study Pharmacy Manual.

Product complaints and medication errors in and of themselves are not AEs. However, AEs or SAEs resulting from a product complaint should be reported.

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14.2.8. Anti-drug Antibodies

As rusfertide is a protein drug, participants may mount an immune response to rusfertide producing ADA. Development of ADA will be monitored throughout the study. Should any participant develop ADA, the impact of ADA on rusfertide's safety and efficacy in that participant will be evaluated.

14.2.9. Other Safety Parameters and Related Information

Additional safety parameters (laboratory tests, 12-lead ECGs, physical examinations, and vital signs) and concomitant medications are collected as shown in the schedules of assessments in Table 6, Table 7, Table 8, and Table 9. Clinical laboratory assessments are listed in Appendix 3.

Abnormal findings, other than PD markers, that are deemed clinically significant or are associated with signs and/or symptoms must be recorded as AEs (or recorded as an SAE if they meet the criteria of being serious) as described previously.

The investigator should exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom.

A clinically significant laboratory abnormality in the absence of clinical signs and symptoms may jeopardize the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

14.3. Recording of AEs and SAEs

14.3.1. Recording of AEs

All AEs will be recorded on the appropriate page of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event. For both serious and nonserious AEs, the investigator or designee must determine:

Severity (toxicity grade) for each AE, including any clinically significant laboratory abnormality, will be determined using NCI CTCAE Version 5.0.

Relationship (ie, causality) of the event to the trial intervention will be assessed by the investigator or designee and recorded in the eCRF using the existing AE relationship/cause field(s), per EDC instructions. Refer to Section 14.2.2.1 for causality definitions.

Outcome at the time of recording, assessed as recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, or unknown.

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14.3.2. Recording of SAEs

All SAEs must be reported to the sponsor within 24 hours of the site becoming aware of the event using the sponsor-designated paper-based SAE form (submitted per the site manual, for example, via email or fax).

SAEs must also be documented in the participant's study records and entered into the eCRF in accordance with the study's data entry procedures (as applicable). Entry into the eCRF does not replace SAE reporting to the sponsor.

Information recorded on the SAE form must be consistent with the clinical data recorded elsewhere in the study records (including the eCRF, if applicable).

Further details on assessing severity and causality of AEs and SAEs are in Section 14.2.2 and 14.2.2.1.

14.4. Reporting Adverse Events

Adverse Events: All AEs, regardless of their relationship to rusfertide, will be reported on the AE CRF. In order to ensure timely safety oversight of the trial, AEs should be reported routinely. All reports should include time of onset and resolution, severity (see Section 14.2.2), relationship to rusfertide, action taken regarding rusfertide and outcome.

Cancer Events Immediately Reportable to the sponsor: All new or recurring cancers that develop after initiation of rusfertide treatment, regardless of seriousness or causality, must be reported to the sponsor within 24 hours from the time the site investigational team first becomes

aware of the event. The Cancer Event report form should be used to report all cancers, serious and nonserious, according to the instructions provided below for SAEs. Cancer events are considered AESIs.

SAEs: In order to meet the requirements for expedited reporting of SAEs to applicable regulatory authorities and IRBs/IECs, all SAEs, must be reported to the sponsor within 24 hours from the time the site investigational team first becomes aware of the event.

Suspected unexpected serious adverse reactions (SUSARs) will be reported to regulatory authorities in accordance with applicable legislation. For EU countries SUSARs will be reported to Eudravigilance.

The SAE report form should be completed as thoroughly as possible and signed by the investigator before transmittal to the study sponsor. It is very important that the investigator provide an assessment of the causal relationship between the event and study drug at the time of the initial report, as this is required for determining the timing for submissions to regulatory authorities.

Initial notification of an SAE by telephone or email must be confirmed in writing 24 hours from the time the site investigational team first become aware of the event using the SAE report form as described above.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form and marked as a follow-up report.

Takeda or their representative is responsible for notifying the relevant regulatory authorities of certain events. It is the principal investigator's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

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14.5. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

Regardless of causality, all AEs must be monitored until the End of Study visit (including the 4-week safety follow-up visit, when applicable), or until the event resolves, stabilizes, is otherwise explained, or the participant is lost to follow-up (see Section 9.3.3 Participant Withdrawal Criteria).

SAEs must be monitored until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.

If information not available at the time of the first SAE report becomes available at a later date, then the investigator will transmit follow-up SAE information using the sponsor-designated SAE reporting mechanism (ie, paper-based SAE form submitted via email or fax, as provided in the site manual) immediately, within 24 hours of receipt. Copies of any relevant data from the

hospital notes (for example, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested

14.6. Emergency Unblinding of Treatment Assignment

The blind in Part 1a may be broken in the event of a medical emergency, if the investigator determines that knowledge of the investigational product identity is critical to the management of the participant's medical emergency. The investigator should not unblind treatment assignment if knowledge of the treatment assignment will not affect the way the participant would be treated. Unblinding will be performed using the IxRS system. It is recommended that the Takeda medical monitor be contacted before the investigator breaks the blind unless this could delay emergency treatment of the participant. In the event of unblinding without contacting the medical monitor first, the Takeda medical monitor should be contacted as soon as possible after the unblinding. The unblinding must be clearly justified and explained by a detailed justification in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding. Participants whose treatment is unblinded before completing Part 1a of this study will be withdrawn from the study.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a participant's treatment assignment is disclosed to the investigator before a participant completes Part 1a, the participant will be withdrawn from the study. The participant should be followed according to early withdrawal procedures (Section 12.2.7).

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14.7. Splenomegaly

Spleen size is assessed using MRI, ultrasound, or CT (in countries where CT is approved) at time points shown in the schedules of assessments (Table 6, Table 7, and Table 8). MRI is the preferred procedure. The window for routine assessment of spleen size is ±4 weeks. Each site's radiology group will measure spleen size.

Worsening splenomegaly is defined as a 30% or greater increase in the longest dimension.

Symptomatic splenomegaly includes fatigue, night sweats, itching, abdominal discomfort, pain under the left ribs, feeling of fullness after eating and bone pain. Investigators should exclude other causes of these symptoms particularly in participants who do not have enlarged spleens on physical examination.

15. PHARMACOKINETIC, PHARMACODYNAMIC AND EXPLORATORY ASSESSMENTS

PK: Blood samples for pharmacokinetics will be obtained pre-dose, approximately 2 to 8 hours post dose, and approximately 20 to 60 hours post dose (C_{max}). These time points will allow comparison of rusfertide plasma concentrations with PD markers, particularly iron parameters (TSAT) measured at the same time points and for preliminary PK analyses. Additional samples will be obtained to measure the trough concentrations on selection visits.

15.1. Blood Sample Collection Schedule

PK samples will be collected pre-dose in Weeks 0, 8, 24, 32, 36, 40, 60, 72, 84, 96, 120, 132, 144, and 156. PK samples will be collected pre-dose and post-dose (2-8 hours and 20-60 hours) in Weeks 16, 52, and 108. An additional PK sample will be collected at the 4-week safety follow-up visit.

PD samples will be collected at the same time points as the PK samples.

15.2. Pharmacokinetic Blood Sample Collection and Processing

See the Laboratory Manual for blood sample labeling, processing, storage, and shipment instructions.

15.3. Exploratory Biomarkers of Interest

Assessment of laboratory markers of interest including but not limited to those listed below may be performed:

- Erythropoietin
- Hepcidin, IL-6, fibrogen d-dimer.
- JAK2 mutation burden
- Additional markers of inflammation, hematopoiesis, and coagulation may be included based on the most recent scientific literature at the time of analysis.

Samples for exploratory biomarkers of interest may be held for up to 10 years. Other than JAK2 mutation burden, no genetic testing will be done.

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15.4. Total Blood Collection - PK, PD, and Clinical Laboratory

It is estimated that approximately 23 PK and PD samples and 9 samples for biomarkers will be collected over the total duration of the study. In addition, blood samples for clinical laboratory will be collected at every scheduled visit.

A total of approximately 701 mL of blood will be collected over about 3 years if the participant completes the entire study.

16. STATISTICS

Primary and key secondary efficacy analyses will be conducted after all participants have completed Part 1a or discontinued Part 1a early. To evaluate durability of response for rusfertide, analyses will be conducted after all participants have completed Part 1b or discontinued Part 1b early. Comprehensive efficacy and safety analyses will be conducted after all participants remaining in the study have either completed the study or discontinued early. A SAP will be

prepared by the sponsor or its designee prior to unblinding. In case of differences between the protocol and the SAP regarding analyses, the SAP will take precedence.

16.1. Study Design and Sample Size Estimation

This is a randomized, placebo-controlled, add-on study followed by an open label treatment period with rusfertide in a long-term extension.

Overall, the study with approximately 250 participants, randomized 1:1 to treatment arms (125 per arm) will have at least 95% power to test the primary endpoint. The primary and key secondary tests, with overall control for Type 1 error, will use $\alpha = 0.05$ (2-sided).

16.1.1. Primary Endpoint

The response rate estimate in RESPONSE trial (Vannucchi 2015) was 19.6% for Best Available Therapy (BAT) and 60% for ruxolitinib. In order not to overestimate the treatment effect for this trial a response rate (absence of phlebotomy-eligibility) of approximately 25% on placebo and 50% from rusfertide during Weeks 20 to 32 (inclusive) was assumed. Based on these assumptions 95 participants will be required per treatment group to detect a difference in the proportion of participants treated with rusfertide achieving clinical response compared to participants treated with placebo at a 0.05 level of significance (2-sided) with approximately 95% power using a z-test based on the large sample normal approximation to binomial distribution. The endpoint will be compared between placebo and rusfertide using the Cochran-Mantel-Haenszel (CMH), stratified by ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other).

This endpoint will be presented as the first key secondary efficacy endpoint for European Medicines Agency (EMA) submissions.

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16.1.2. Key Secondary Endpoints

16.1.2.1. Mean Number of Phlebotomies between Week 0 through Week 32 (Inclusive)

The objective is to evaluate the efficacy of rusfertide in maintaining hematocrit control. Based on available data from a phase 2 study, PTG-300-04, it is observed during the open-label dose-finding part of the study, the mean number of phlebotomies in 16 weeks prior to treatment with rusfertide is approximately 2.8 and in the 16 weeks post-treatment with rusfertide is approximately 0.17. Considering these average phlebotomies prior to treatment with rusfertide as placebo and post-rusfertide as on treatment and accounting for the extended duration of 32 weeks, it is assumed that for the double-blind treatment the mean number of phlebotomies to be approximately 3 and 1 for placebo and rusfertide over 32 weeks, respectively, with a standard deviation of 4. Based on these assumptions 106 participants will be required per treatment group to detect a treatment difference in mean number of phlebotomies between the placebo and rusfertide treatment arms at a 0.05 level of significance (2-sided) with at least 95% power using a two-sample t-test.

As part of advice from the EMA, this endpoint will be presented as the primary efficacy endpoint for European submissions.

16.1.2.2. Proportion of Participants with All Hematocrit Values <45% between Week 0 through Week 32 (Inclusive)

Important considerations in PV management include maintaining hematocrit <45% and controlling clinical symptoms. Clinical studies indicate that more than 1 in 4 participants have hematocrit ≥45%. This key secondary endpoint will be compared between placebo and rusfertide using CMH test stratified by ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other) to detect a treatment difference. It is assumed that approximately 60% of the participants treated with rusfertide will have all hematocrit values <45% between Week 0 through Week 32 (inclusive), with a single transient hematocrit value ≥45% being allowed compared to 35% for placebo-treated participants starting at Week 0 and continuing through Week 32. Based on these response rate assumptions, 106 participants will be required per treatment group to detect a difference between rusfertide and placebo for this endpoint with at least 95% power with a 5% 2-sided level of significance using a z-test based on the large sample normal approximation to binomial distribution.

16.1.2.3. Mean Change from Baseline in Total Fatigue Score Based on PROMIS Short Form 8a at Week 32

Fatigue is considered as one of the most common, severe and debilitating symptoms across MPNs (Myeloproliferative Neoplasms [MPNs] Landmark Survey). Based on a survey of 538 with PV (Emanuel 2012), fatigue carried the highest symptom intensity using the MPN-SAF 10 (mean = 4.4 with standard deviation of 2.8). Given the impact of this symptom on the participants' functionality the mean change from baseline in total fatigue score based on PROMIS Short Form 8a will be compared between rusfertide and placebo. Assuming a standard deviation of 2.8 units, a sample size of 125 in each group will have at least 80% power using a two-sample t-test to detect a difference of a 1-unit change from baseline with a 0.05 2-sided level of significance.

16.1.2.4. Mean Change from Baseline in Total Score Based on MFSAF v4.0 at Week 32

The MFSAF v4.0 is a 7-item questionnaire which allows for the assessment of patient-reported symptom manifestation (Gwaltney 2017). Assuming a standard deviation of 5.5 units a sample size of 125 in each group will have at least 80% power using a two-sample t-test to detect a difference of a 2-unit change from baseline with a 0.05 2-sided level of significance.

16.1.3. Closed Testing Procedure — Single Hierarchical Order

The fixed-sequence method will be employed to address multiple endpoint-related multiplicity. The endpoints are ordered in a pre-defined sequence and the family-wise error rate will be controlled at 0.05 level of significance for the primary endpoint and the 4 key secondary endpoints with treatment difference in favor of rusfertide.

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If the primary endpoint is statistically significant at a 2-sided 0.05 level of significance, the 1st key secondary will be tested at a 2-sided 0.05 level of significance using Analysis of Covariance (ANCOVA) with number of phlebotomies in 6 months prior to randomization as a covariate and treatment and stratum as factors. If the 1st key secondary endpoint is significant then the 2nd key secondary endpoint will be compared between rusfertide and placebo using CMH at a 2-sided 0.05 level of significance with adjustment for stratification factor. If the 2nd key secondary endpoint is significant then the 3rd key secondary endpoint of treatment difference between rusfertide and placebo will be analyzed for mean change from baseline in total PROMIS T-score at Week 32 at a 2-sided 0.05 level of significance using a mixed model for repeated measures (MMRM) model and will include treatment and stratification as fixed factors and baseline score as a covariate. If the 3rd key secondary is significant then 4th key secondary endpoint of mean change from baseline in MFSAF v4.0 TSS7 at Week 32 at 2-sided 0.05 level of significance will be evaluated for treatment difference between rusfertide and placebo using an MMRM model and will include treatment and stratification as fixed factors and baseline score as a covariate.

As part of advice from the EMA, the 1st key secondary endpoint, the mean number of phlebotomies between Week 0 through Week 32 (inclusive) will be presented as the primary efficacy endpoint for European submissions. For the European submission the phlebotomy eligibility endpoint (Section 16.1.1) will be the first key secondary endpoint in the hierarchy for the closed testing procedure.

No alpha adjustment will be made for the remaining secondary endpoints.

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16.2. Demographics and Baseline Characteristics

The demographics and baseline characteristics will be summarized using descriptive statistics and frequency. Demographics information includes age, sex, and race. Baseline disease characteristics include but are not limited to phlebotomies prior to enrollment, risk category, allele burden and cytoreductive therapy.

16.3. Analysis of Efficacy Data

The efficacy analysis will be conducted for Parts 1a, 1b, and 2 separately as well as combined to assess maintenance of effect. Efficacy in Part 3 will be summarized as appropriate using descriptive statistics.

Baseline is defined as the last assessment done on the date prior to or the same date of the first dose of study drug, unless otherwise specified. For MFSAF v4.0, the baseline will be the average score of the 7-day interval immediately on or prior to first dose date. The weekly total symptom score at each scheduled visit will be calculated by averaging daily total symptom scores over a 7-day interval during the week leading to the scheduled visit (inclusive).

The primary efficacy analysis period is Part 1a. During this period participants will be randomized 1:1 to rusfertide and placebo for 32 weeks. Comparison between placebo and rusfertide will be conducted during this period for the primary efficacy and key secondary efficacy endpoints.

Part 1a and Part 1b combined will be for 52 weeks. The 32 weeks in Part 1a will be double-blind and the 20 weeks in Part 1b will be open label. These two parts combined will be utilized to evaluate the durability of effect of rusfertide over 52 weeks.

For all efficacy analyses by subgroup (for example, gender, risk category, concurrent cytoreductive therapy), the same analysis methods as described above will be applied. In Part 1a and Part 1b, the dose of cytoreductive therapy may be decreased or stopped for safety. However, an increase in dose for efficacy (for example, to control hematocrit, platelets, and/or WBC) will not be allowed, and participants cannot start new cytoreductive therapy. In Part 2 and Part 3, the dose of cytoreductive therapy may be adjusted up or down for both safety and efficacy. Participants may also start new cytoreductive therapy (hydroxyurea, interferon, ruxolitinib or other approved JAK inhibitor) in Part 2 and Part 3. The impact of changes in the ongoing cytoreductive therapy during the study on the efficacy endpoints will be evaluated.

16.3.1. Analysis of Primary Efficacy Endpoint

Proportion of participants achieving a response starting at Week 20 through Week 32 (inclusive) is the primary endpoint to evaluate the efficacy of rusfertide compared to placebo. A response is defined as absence of phlebotomy eligibility. Phlebotomy eligibility is defined as **either** a confirmed hematocrit ≥45% and that is at least 3% (absolute) higher than the baseline hematocrit **or** a hematocrit ≥48%. Confirmation is defined as 2 consecutive hematocrit assessments that are ≥45% and at least 3% higher than the baseline hematocrit.

Hematocrit values from each clinical site's local laboratory will be used for the primary endpoint.

The ITT will be used for the primary efficacy analysis.

The primary efficacy endpoint of difference in proportions between rusfertide and placebo at Week 32 will be analyzed using Cochran-Mantel-Haenszel (CMH) test at a 0.05 2-sided level of significance, stratified for ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other).

If a participant becomes phlebotomy eligible prior to Week 20 but maintains absence of phlebotomy eligibility between Week 20 and Week 32 (both inclusive) the participant will be considered as a responder. Participants who may be classified as non-responders are defined in Section 16.6. The overall stratum-adjusted odds ratio will be used as a measure of association between treatment and response.

As part of advice from the EMA, it is proposed the first key secondary endpoint described in Section 16.3.2, average number of phlebotomies between Week 0 through Week 32 (inclusive) be presented as the primary efficacy endpoint for European submissions.

16.3.2. Analysis of Key Secondary Endpoints

The four key secondary endpoints will be tested for treatment differences through closed testing procedure in a single hierarchical order as described in Section 16.1.3. The ITT will be used for the key secondary efficacy analysis.

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16.3.2.1. Mean Number of Phlebotomies between Week 0 through Week 32 (Inclusive)

Analysis of covariance (ANCOVA) will be used to estimate the treatment effect. The model will include the number of phlebotomies in 6 months prior to randomization as a covariate and fixed effects of treatment, and stratification. The comparison will be based on the difference in least squares mean between treatments between Week 0 and Week 32 (inclusive).

This endpoint will be used as the primacy efficacy analysis for European submissions.

16.3.2.2. Proportion of Participants with All Hematocrit Values <45% between Week 0 through Week 32 (Inclusive)

A single hematocrit value ≥45% between Week 0 and Week 32 will be allowed. This endpoint will be analyzed similar to the primary endpoint using CMH 2-sided test at a 0.05 level of significance, stratified for ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other).

16.3.2.3. Mean Change from Baseline at End of Part 1a (Week 32) in the PROMIS Fatigue Short Form 8a Total T-score

The mean change from baseline in total fatigue T-score using PROMIS Short Form 8a will be analyzed using a MMRM model and will include treatment and stratification as fixed factors and baseline score as a covariate. The model will use an unstructured within participant covariance matrix and a ReML estimation method. Details will be outlined in the SAP.

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16.3.2.4. Mean Change from Baseline at End of Part 1a (Week 32) in the Total MFSAF TSS7

The baseline for the MFSAF v4.0 TSS7 will be the mean score based on the 7-day interval immediately prior to randomization. The weekly total symptom score will be calculated by averaging daily scores over a 7-day interval leading to Week 32 (inclusive). The mean change from baseline in TSS7 will be analyzed using an MMRM model that will include treatment and stratification as fixed factors and baseline score as a covariate. The model will use an unstructured within participant covariance matrix and a ReML estimation method. Details will be outlined in the SAP.

16.3.3. Analysis of Other Secondary Endpoints

All categorical efficacy endpoints will be analyzed using CMH test at a 0.05 2-sided level of significance, with adjustment for stratification factor of ongoing PV therapy (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other). Participants who discontinue prematurely or have missing data at a scheduled assessment time point will be considered non-responders for that endpoint.

Continuous endpoints such as average of number of phlebotomies will be analyzed using ANCOVA with the number of phlebotomies in 6 months prior to randomization as a covariate and treatment and stratification as main effects.

Mean changes from baseline will be analyzed using MMRM. The model will include the fixed effects of treatment and stratification and baseline scores as covariate. The comparison will be based on the difference in least squares mean between treatments at the specific time point.

Mean changes from baseline in EORTC QLQ-C30 score for each of the 5 functional scales, 3 symptomscales, 1 global health status/QoL scale, and 6 single-item scales at Week 32 will be summarized descriptively. Baseline is defined as the score obtained during Screening. The scores for each scale are calculated based on responses from the 30 questions. Detailed algorithm will be provided in the SAP.

To estimate the time to event such as phlebotomy or hematocrit value ≥45% Kaplan-Meier estimate will be presented and a stratified log-rank test will be used to compare treatment arms.

The ITT population will be used for the analysis of other secondary endpoints. No multiplicity adjustments will be made for other secondary endpoints.

Part 1a - Week 0 through Week 32 (inclusive):

Comparison of rusfertide to placebo during randomized, double-blind, placebo-controlled, add-on parallel phase

PV-focused PRO-related secondary endpoints in participants with moderate or severe symptoms:

- Mean change from baseline at end of Part 1a (Week 32) in the PROMIS Fatigue Short Form 8a total T-score among participants who have moderate or severe symptoms at baseline.

  The PROMIS Fatigue SF 8a T-score will be obtained via the Item-Response Theory (IRT) response-pattern scoring approach using the PROMIS Scoring Service available at https://www.assessmentcenter.net/ac_scoringservice. The calibration sample is the default "PROMIS Wave 1" (Cella 2010). Moderate or severe symptoms are defined as a baseline PROMIS Fatigue SF 8a total T-score ≥58.8 based on descriptive analysis approach described in PAP v2.0. In the descriptive analysis approach the distribution of the PROMIS Fatigue SF 8a total T-score at Baseline was categorized using the PGI-S. The response quartiles were used to establish the recommended cut-off points for the PROMIS Fatigue SF 8a total T-score corresponding to "none" or "mild" versus "moderate" or "severe" categories on the PGI-S. Analysis similar to the key secondary endpoint described in Section 16.3.2.1 will be conducted.

- Mean change from baseline at end of Part 1a (Week 32) in the MFSAF TSS4 among participants who have moderate or severe symptoms at baseline. TSS4 is the sum of 4 items of the MFSAF (fatigue, itching, night sweats, and abdominal discomfort). The weekly TSS4 at Week 32 will be calculated by averaging daily TSS4 over a 7-day interval leading to Week 32 (inclusive).

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The MFSAF TSS4 is the sum of four items in the MFSAF (fatigue, itching [pruritis], night sweats, and abdominal discomfort). The weekly TSS4will be calculated by averaging daily scores over a 7-day interval leading to Week 32 (inclusive). Moderate or severe symptoms are defined as a baseline MFSAF TSS4 ≥9.1 based on descriptive analysis approach described in PAP v2.0. In the descriptive analysis approach the distribution of the MFSAF TSS4 at Baseline was categorized using the PGI-S. The response quartiles were used to establish the recommended cut-off points for the MFSAF TSS4 corresponding to "none" or "mild" versus "moderate or "severe" categories on the PGI-S. Analysis similar to the key secondary endpoint described in Section 16.3.2.2 will be conducted.

- Mean change from baseline at end of Part 1a (Week 32) in the MPN-SAF Problems with Concentration among participants who have moderate or severe symptoms at baseline.

  Moderate or severe symptoms are defined as a baseline MPN-SAF problems with concentration ≥ 4 (Emanuel 2012). This definition of moderate or severe symptoms was also confirmed based on descriptive analysis approach described in PAP v2.0. In the descriptive analysis approach the distribution of the MPN-SAF problems with concentration at Baseline was categorized using the PGI-S. The response quartiles were used to establish the recommended cut-off points for the MPN-SAF Problems with Concentration corresponding to "none" or "mild" versus "moderate or "severe" categories on the PGI-S.

  The mean change from baseline in MPN-SAF problems with concentration will be analyzed using an MMRM model that will include treatment, scheduled visit, and stratification variable (phlebotomy only, phlebotomy+hydroxyurea, phlebotomy+ruxolitinib, phlebotomy+interferon, phlebotomy+other) as fixed factors, treatment-by-visit interaction, baseline-by-visit interaction, and baseline MPN-SAF problems with concentration as a covariate. The model will use an unstructured within participant covariance matrix and a ReML estimation method. The degree of freedom of the denominator will be estimated using the Kenward-Roger method. The primary contrast of interest is the least squares mean difference between rusfertide and placebo at Week 32.

  If the model fails to converge using an unstructured covariance matrix, a simpler covariance structure (for example, TOEPH, ARH(1) and AR(1), in that order) may be employed to achieve convergence.

- Proportion of participants with a meaningful within-person change at Week 32 in the PROMIS Fatigue SF8a T-score, MFSAF TSS4, and MPN-SAF problems with concentration among participants who have moderate or severe symptoms at Baseline

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Other PRO-related secondary endpoints

- Mean change from baseline at each scheduled assessment in individual questions and the total T-score based on PROMIS® Short Form 8a T-score.
- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MFSAF v4.0.
- Proportion of participants with a meaningful within-person change at Week 32 in the PROMIS Fatigue SF 8a T-score, MFSAF TSS4, and MPN-SAF problems with concentration.
- Mean change from baseline in PGI-S at each scheduled assessment.
- Proportion of participants with at least one unit improvement in the PGI-S, that is., a ≥1 point decrease in the PGI-S, for example, a change from "Moderate (2)" to "Mild (1)" or "Mild (1)" to "None (0)" at each scheduled visit.
- Proportion of participants with a rating on the PGI-C of either "much better" or "a little better" at each scheduled assessment.
- Average PGI-C at each scheduled assessment.
- Mean change from baseline at each scheduled assessment in individual symptom score and the total score based on MPN-SAF TSS 10.
- Mean change from baseline in the individual domain scores and the total EORTC QLQ-C30 score at Week 32.

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Hematocrit and Phlebotomy-related secondary endpoints

- Median time to first hematocrit ≥45% after randomization.
- Proportion of participants with at least one hematocrit ≥48%.
- Proportion of participants who maintain absence of phlebotomy eligibility.

Parts 1a+1b: Week 0 through Week 52

- Proportion of participants originally randomized to rusfertide achieving absence of phlebotomy eligibility (durable response) for ≥52 weeks.
- Median time to first hematocrit ≥45% during Part 1b excluding Part 1a.
- Median time to first phlebotomy during Part 1b excluding Part 1a.

Parts 1a+1b+2: Week 0 through Week 156

The main goal of Part 2 is to evaluate maintenance of effect and safety during the extended period of treatment until Week 156. No hypothesis testing will be performed for Part 2. Where appropriate, point estimate and the confidence interval associated with the estimate will be provided.

Part 3: Week 156 through End of Study

Safety and efficacy in Part 3 will be summarized as appropriate using descriptive statistics.

16.4. Sensitivity Analysis of the Primary and Key Secondary Endpoints

16.4.1. Full Analysis Set

The primary and the key secondary endpoints will be analyzed as outline in Section 16.3.1 and Section 16.3.2 using the FAS (Section 16.5.2).

16.4.2. Per Protocol Analysis

The primary and the key secondary endpoints will be analyzed as outlined in Section 16.3.1 and Section 16.3.2 using the PPS (Section 16.5.4).

16.4.3. Single Point Imputation

The continuous key secondary endpoints will be analyzed as outlined in Section 16.3.2. Missing data will be imputed by last observation carried forward (LOCF) and baseline observation carried forward (BLOCF). This analysis will be performed using the intent-to-treat (ITT) (Section 16.5.1).

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16.4.4. Tipping Point Analysis

Tipping point analysis, based on ITT, will be employed to assess the robustness of the results under the missing not at random assumption.

Analysis for the categorical endpoints will follow the algorithm for the binary variable (responder/non-responder). This analysis will include all observed data and then vary assumptions about the missing outcomes, by assigning responders to some of the missing data and non-responder to the remaining missing data in the two treatment arms. The tipping point will be defined as the difference in the proportion of responders at Week 32 between the two treatment groups in the missing part at which the result changes.

In the analysis for the continuous endpoints, participants who withdraw from the rusfertide treatment arm or have missing observations at Week 32 are assumed to have an effect that is inferior to the observed values. The extent of the penalty will be gradually increased to evaluate the point at which the result is not statistically significant (tipping point). Details will be provided in the SAP.

16.5. Analysis Populations

16.5.1. Intent-to-Treat (ITT)

All randomized participants according to the treatment assigned at randomization. Intercurrent events will be defined in the SAP.

16.5.2. Full Analysis Set (FAS)

All randomized participants according to the treatment assigned at randomization (ITT) and have a baseline and at least one postbaseline assessment in Part 1a.

16.5.3. Safety Analysis Set (SAS)

All randomized participants who receive at least one dose of study drug. Adverse events that start on or after the randomization date will be considered treatment emergent. This population will be used for all safety analyses. Participants will be analyzed according to the study treatment they actually receive.

16.5.4. Per Protocol Set (PPS)

Subset of participants in ITT who have received at least one dose of study drug with no major protocol deviations that impact efficacy at study entry or during the study. This will include:

- Meeting all inclusion criteria and not meeting any exclusion criterion
- Actual study drug assignment at randomization
- Participants with no more than 6 missed doses in 32 weeks and/or no more than 2 consecutive missed doses in 32 weeks in Part 1a.
- Not taking any prohibited medications or prohibited changes in cytoreductive therapy during the 32 weeks.

Additional criterion may be defined prior to unblinding in the SAP. This set will be used supportive analyses for the primary and key secondary endpoints.

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16.5.5. PK/PD Analysis Set (PKPDAS)

Subset of participants in ITT who have received at least one dose of study drug and have at least one post-baseline PK/PD assessment.

16.6. Handling of Missing Data and Definition of Non-Responders

The primary efficacy analysis will be conducted on the ITT. Post-randomization missing data will be imputed as a “non-response” for the primary efficacy endpoint.

A non-responder includes the following:

- Participant is missing hematocrit assessment at Week 32; or
- Participant discontinues the study treatment prematurely during Part 1a; or
- Participant has more than 1 missing hematocrit value at any scheduled visit between Week 20 and Week 32 (inclusive). The hematocrit value may be obtained within ±1 week of the scheduled visit; or
- Participant is phlebotomized between Week 20 and Week 32 (inclusive); or

Participant with hematocrit ≥45% and that is at least 3% higher than the baseline hematocrit at Week 32 (that is, no confirmation is required at Week 32).

For the key secondary endpoints:

1. Average number of phlebotomies between Week 0 and Week 32 (inclusive):

   Phlebotomy data available prior to randomization will be utilized for participants who discontinue Part 1a earlier than completing Week 32. It will be assumed that the participants continue to observe the same number of phlebotomies, that is, no treatment benefit during the study. Based on this assumption, the number of phlebotomy events prior to randomization will be normalized to 32 weeks and will be imputed under the assumption that the distribution of missing values during Week 0 through Week 32 is the same as that of observed values prior to randomization.

2. Proportion of participants with all hematocrit values between Week 0 through Week 32 (inclusive). A single hematocrit value ≥45% is allowed:

   A participant will be considered as non-responder if:

   - Participant is missing a hematocrit assessment at Week 32 and had at least one value ≥45% prior to Week 32 or
   - Participant discontinues the study treatment prematurely during Part 1a
   - Participant has more than two missing hematocrit values at any scheduled visit between Week 0 and Week 32 (inclusive). The hematocrit value may be obtained within ±1 week of the scheduled visit.
   - If a participant is phlebotomized between Week 0 and Week 32 (inclusive).

3. Mean change from baseline in the total fatigue T-score based on PROMIS Short Form 8a T-score at Week 32:

   An MMRM approach will be employed to use all available visit data, including participants with some missing visit data in order to arrive at an estimate of the mean treatment effect.

4. Mean change from baseline in the Total MFSAF v4.0 TSS7 score at Week 32:

   The weekly total symptom score will be calculated by averaging daily scores over a 7-day interval leading to Week 32 (inclusive).

   - If 4 or more days of data are missing during the week the score will be considered missing.

   An MMRM approach will be employed to use all available visit data, including participants with some missing visit data in order to arrive at an estimate of the mean treatment effect.

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Similar analysis approach as the key secondary endpoints will be used to analyze the PV-focused PRO-related endpoint in participants with moderate or severe symptoms at baseline.

For the other secondary endpoints:

In general, for the categorical secondary endpoints if a participant is missing a value for an assessment at a visit in Part 1a, he/she will be considered a non-responder for that endpoint at the specific time point. Missing data will not be imputed for calculation of mean changes and other quantitative analyses.

16.7. Analysis of Safety

Quantitative safety data will be summarized using descriptive statistics and frequency distributions. Qualitative safety data will be summarized by frequencies and percentages. All summaries will be presented by treatment arms. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA®), Concomitant medications will be coded using World Health Organization (WHO) drug dictionary.

Laboratory evaluations, vital signs assessments and ECG parameters will be summarized by treatment group and protocol specified collection time point. A summary of change-from-baseline at each protocol specified time-point by treatment group will also be presented.

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16.8. Analyses of Pharmacokinetics and Pharmacodynamics

Individual rusfertide concentration data will be listed and summarized by treatment group with descriptive statistics (number, arithmetic mean, standard deviation, median, minimum, maximum and geometric mean). Individual and mean rusfertide concentration-time profiles for the rusfertide group will also be presented graphically.

Serum samples will be evaluated for the presence of ADA through the use of an immunoassay. If ADA is detected in clinical samples, the effect of ADA on PK, safety and efficacy will be explored.

Pharmacodynamics will be listed for each individual and summarized by frequency counts for discrete categories. Individual data will be listed for each individual and summarized by nominal sampling time point and treatment group with descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum). A summary of change-from-baseline at each protocol specified time-point by treatment group will also be presented.

17. ADMINISTRATIVE PROCEDURES AND ETHICAL CONSIDERATIONS

17.1. Audits and Inspections

Authorized representatives of Takeda, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Takeda audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Takeda immediately if contacted by a regulatory agency about an inspection.

17.2. Study Monitoring and Inspection of Records

Takeda or their designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

At intervals during the study, as well as after the completion of participant enrollment, the study center will be monitored by a clinical research associate for compliance, which will include ensuring that study procedures are being followed, ensuring that accurate and complete data are recorded on CRFs, and reviewing source documentation and drug accountability records.

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17.3. Guidelines for Good Clinical Practice

This study will be conducted in accordance with principles of GCP as promulgated by the ICH. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of human participants are protected under current ethical principles, and that the clinical trial data are credible. Current GCP standards may be found in ICH Guidance E6 (Good Clinical Practice: Consolidated Guidance). This guidance describes the principles of GCP and the obligations of the IRB/IEC, the investigator and the sponsor in conducting this study in accordance with those principles.

17.4. Protocol Deviations

investigators will apply due diligence to avoid protocol deviations. Except as noted in the Disaster Plan (Appendix 4) the investigator should not contact the sponsor or its agents to request a protocol deviation, as authorized deviations are not allowed. However, the investigator is expected to take any immediate action required for the safety of any participant, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of

this action and the IRB/IEC or similar body at the study site should be informed within 10 working days.

All major protocol deviations will be recorded and reported in the CSR.

17.5. Ethics

17.5.1. Ethics Review

Prior to the commencement of the study, written approval will be required by the relevant IRB or IEC responsible for the investigational site.

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. In addition, the IRB or IEC must approve the IB and all patient facing information including advertising used to recruit patients for the study. The investigator must submit written approval to Takeda before he or she can enroll any patient/participant into the study.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from this or any other study conducted with the investigational product. Takeda will provide this information to the principal investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

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17.5.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable laws and regulations.

17.5.3. Written Informed Consent

A properly executed, written ICF, in compliance with the Declaration of Helsinki, ICH GCP, and US Code of Federal Regulations for Protection of Human Participants (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A), will be explained to and signed by each participant prior to entering the trial. The investigator will provide a copy of the signed ICF to each participant and will maintain a copy in the participant's record file.

17.6. Early Site Closure or Trial Termination

17.6.1. Decision Rights for Site Closure and Trial Termination

The sponsor may suspend or terminate the trial, or part of the trial, at any time for any reason. The sponsor reserves the right to close the trial site at its sole discretion. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

17.6.2. Criteria for Early Trial Site Closure

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- For trial termination:
  - Discontinuation of further trial intervention development.
- For trial site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator.
  - Total number of participants included earlier than expected.

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17.7. Case Report Forms

Site personnel should collect and record data for the study as source documents and transfer the data into the CRF.

The investigator must ensure that complete data for the clinical study are collected and accurately documented in the appropriate sections of the CRF and adequately supported by the appropriate source documentation. In addition, it is the investigator's responsibility to provide signatures where requested indicating concurrence with data in the CRF.

17.8. Retention of Records

International Conference on Harmonization, GCP, and US Food and Drug Administration guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

However, the essential documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. Records should never be destroyed without written approval from the sponsor.

If an investigator leaves the institution, he/she must transfer responsibilities for record retention to another individual willing to accept them. The investigator must notify the sponsor in writing of the transfer of study documents before the transfer of the study.

17.8.1. Introduction

Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the List of Investigator Responsibilities in Section 17.8.2.

The trial is being funded by Takeda. Payments for the conduct of the trial that will be made to trial sites (and, if applicable, investigators and/or other trial staff) will be specified in the Clinical Trial Site Agreement(s). All investigators and subinvestigators must declare potential conflicts of interests to the sponsor. The sponsor will provide a financial disclosure form that must be signed by each investigator and subinvestigator before the trial starts at their trial site; in addition, any potential conflicts of interests that are not covered by this financial disclosure form should be disclosed separately to the sponsor before the start of the trial at their site.

All institutional affiliations of the investigator and subinvestigator should be declared on their curriculum vitae, which must be provided to sponsor before the start of the trial.

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17.8.2. List of Investigator Responsibilities

Clinical research trials sponsored by the sponsor are subject to ICH GCP and all applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the Statement of Investigator (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that trial-related procedures, including trial-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential participants before the receipt of written approval from relevant governing bodies/authorities.

5. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to participants. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed (e)consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed (e)consent from each trial participant, and document the date of (e)consent in the participant's medical chart. Valid informed (e)consent is the most current version approved by the IRB/IEC. Each ICF should contain a participant authorization section that describes the uses and disclosures of a participant's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a participant authorization, then the investigator must obtain a separate participant authorization form from each participant or the participant's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied trial interventions, and return all unused sponsor-supplied trial interventions to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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17.8.3. Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (for example, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.

- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other trial interventions used in other clinical trials that may contain the same chemical compound present in the trial intervention.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting investigator site contact information, trial details, and results on publicly accessible clinical trial registries, databases, and websites.

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The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in the investigator's own country.

The investigator acknowledges and consents to the use of this personal information by Takeda and other parties for the purposes described above.

18. PUBLICATION AND CLINICAL TRIAL REGISTRATION AND DISCLOSURE POLICIES

During and after the trial, only the sponsor may make trial information available to other trial investigators or to regulatory agencies, except as required by law or regulation.

18.1. Publication Policy

The sponsor may publish any data and information from the trial (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication venue (for example, congress, journal) will appropriately reflect contributions to the production, review, and approval of the document.

18.2. Clinical Trial Registration and Disclosure

Per Takeda's policy/standards and applicable laws, regulations, and guidance, Takeda will

- register clinical trials on ClinicalTrials.gov, or other publicly accessible websites and registries, as applicable

and

- disclose the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites (such as clinicaltrialsregister.eu) including the Takeda corporate site.

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20. APPENDICES

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APPENDIX 1. 2016 WHO DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

Major Criteria:

1. Hemoglobin >16.5 g/dL (men) / hemoglobin >16.0 g/dL (women) or hematocrit >49% (men) / hematocrit >48% (women) or increased red cell mass (RCM)[a].
2. 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).
3. Presence of JAK2 V617F or JAK2 exon 12 mutation.

Minor Criteria:

1. Subnormal serum erythropoietin level.

A polycythemia vera diagnosis requires meeting either

- **all three major** criteria

OR

- the **first two major** criteria and **one minor** criterion.[b]

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[a] More than 25% above mean normal predicted value.

[b] Major criterion number 2 (bone marrow biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Source: Barbui T, Thiele J, Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J. 2018;8(2):15 Published 2018 Feb 9. doi:10.1038/s41408-018-0054-y.

APPENDIX 2. CONTRACEPTIVE AND BARRIER GUIDANCE

Participants must follow contraceptive measures as outlined in Section 9.1 Inclusion Criteria and Section 10.9 Contraception.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **Premenarchal**

  A premenarchal state is one in which menarche has not yet occurred.

- **Postmenopausal**

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- **Permanently Sterile**

  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

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Approved methods of contraception for WOCBP are detailed in the table below.

Approved methods of contraception for male participants with WOCBP partners include vasectomy OR WOCBP partner using a highly effective contraceptive method as detailed in the table below. In addition, male participants should use a condom until 90 days following the last dose of study drug.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner *(Vasectomized partner is a highly effective method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of birth control should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable • Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable • Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

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APPENDIX 3. CLINICAL LABORATORY TESTS

HEMATOLOGY (LOCAL AND CENTRAL LABORATORY)

hemoglobin	white blood cell count	absolute neutrophils
hematocrit	% neutrophils	absolute lymphocytes
red blood cell count	% lymphocytes	absolute monocytes
red cell distribution width (RDW)	% monocytes	absolute basophils
reticulocytes (Parts 1a, 1b, and 2 central only; Part 3 local only)		
mean corpuscular volume (MCV)	% basophils	absolute eosinophils
mean corpuscular hemoglobin content (MCHC)	% eosinophils	platelet count
mean corpuscular hemoglobin (MCH)		

CHEMISTRY (CENTRAL LABORATORY [LOCAL LABORATORY FOR PART 3])

sodium	calcium	indirect bilirubin
potassium	phosphorous	alkaline phosphatase
chloride	albumin	alanine aminotransferase (ALT, SGPT)
bicarbonate	total protein	aspartate aminotransferase (AST, SGOT)
blood urea nitrogen (BUN)	uric acid	lactate dehydrogenase (LDH)
creatinine	total bilirubin	estimated glomerular filtration rate (eGFR)
glucose	direct bilirubin	

URINALYSIS (CENTRAL LABORATORY)

pH	ketones	bilirubin
specific gravity	leukocyte esterase	urobilinogen
blood	nitrite	
glucose	protein	

If blood, nitrite, protein, and/or leukocyte esterase abnormalities are noted, a microscopic examination for RBC, WBC, bacteria, casts, crystals, mucous, yeast, and squamous epithelial cells will be performed.

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COAGULATION (CENTRAL LABORATORY)

International normalized ratio (INR)

Prothrombin time (PT)

Partial thromboplastin time (PTT)

PREGNANCY TEST (LOCAL AND CENTRAL LABORATORY)

Serum pregnancy test (Central)

Urine pregnancy test (Local)

OTHER TESTS (CENTRAL LABORATORY)

JAK2 mutation

Hepatitis B surface antigen (HBsAG)

Hepatitis B core antibody (HBc)

Hepatitis C antibody

Human immunodeficiency virus (HIV) antibody

Participants who are negative for HBsAG and positive for HBc will have HBV DNA testing.

Participants positive for Hepatitis C will have hepatitis C RNA testing.

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PHARMACODYNAMIC MARKERS (CENTRAL LABORATORY)

Ferritin

Serum iron

Transferrin

Transferrin saturation (TSAT)

APPENDIX 4. COVID-19 AND OTHER DISASTER MANAGEMENT

This appendix describes actions that may be taken during the coronavirus disease 2019 (COVID-19) pandemic or other disasters that disrupt study operations to manage such operational disruptions in order to preserve the integrity of the study and to ensure participant safety. It will also be applicable in the case of any other potential natural disasters such as floods and typhoons that may disrupt normal study operations. The highest priority is maintaining safety of participants. The goal is further to maintain assessment of study endpoints to the greatest extent possible. Emergency measures can only be used in situations where such a course of action is consistent with the current situation in a particular country and also consistent with up-to-date opinions of local authorities, recommendations and applicable legislation. Takeda will work with each site in a manner that addresses that site's unique situation.

Areas that may be disrupted and approaches to the disruption include, but are not limited to, the following:

1. **Study Visits:** Since participants may not be able to come to the investigational site for protocol-specified visits, sites may use alternative methods for study assessments (for example, phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers). Takeda and the site will determine and document whether the alternatives are necessary, feasible and sufficient to ensure participant safety and to meet study goals.

   Visit windows may be up to ±7 days.

2. **Laboratory Assessments:**

   a. Local laboratories at study sites are normally used to monitor hematocrit levels and perform urine pregnancy tests and a central laboratory is used for other safety laboratory tests (for example, chemistries), and exploratory studies (for example, PK/PD, ADA, inflammatory markers). When blood collection at the study site is not feasible, an outside local clinical laboratory may be used for safety monitoring, including CBC. Normal ranges for the outside local laboratory tests should be obtained.

   b. If possible, outside local laboratories will send blood samples to the central laboratory for exploratory markers, chemistries, urinalysis and confirmatory CBC. However, this is not required. The site should submit a blood sample for ADA at the participant's next clinic visit.

   c. A trained phlebotomist may also be sent to the participant's home to collect blood for shipping to the central laboratory or processing at an outside local laboratory.

3. **Consent:** In all cases, it is critical that participants are kept informed of changes to the study and monitoring plans that could impact them. Revised consent forms should be

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submitted to the Ethics Committees. Participants should give appropriate consent before implementing protocol changes.

a. Options for obtaining consent when participants cannot visit the investigational site include signed consent forms returned by regular mail or email.

b. Alternatively, verbal consent is acceptable provided there is an impartial third-party witness to the consent, the informed consent is explained fully, the participant's questions are answered fully and verbal consent is fully documented. In the event of verbal consent, written consent should be obtained as soon as feasible.

c. Consult with medical monitor to discuss whether remote consent signing is an option in the case of an emergency situation consistent with local regulations.

4. **Study Drug Distribution:** Shipping of study drug from a hospital pharmacy or from a central depot to a participant is allowed if the participant cannot visit the clinic to pick up the study drug. The ability to provide home delivery of study drug may vary by country and region. In all cases, requirements under FDA and other Competent Authority regulations for maintaining required investigational product storage conditions and investigational product accountability remain unchanged.

5. **COVID-19 Testing:** Testing for COVID-19 is not required for this study but may be performed at the investigator's discretion. Payment for COVID-19 testing will be provided by the sponsor. Participants who have COVID-19 infection during screening will be considered screen failures because they have a serious medical condition that would affect compliance with the study procedures. If a participant becomes infected with COVID-19 while participating in the study, the event should be reported as an AE or SAE if the event meets SAE criteria. The participant may continue participating in the study. However, the participant may be withdrawn from the study if it is in the participant's best interest or if the infection will impair compliance with protocol procedures.

6. **COVID-19 Vaccination:** COVID-19 vaccinations are allowed during the study and must be documented in the Concomitant Medications section.

7. **Endpoints:**

a. This study's endpoints are based on changes in hematocrit and requirements for phlebotomy. Use of different clinical laboratories may affect assessment of changes in hematocrit and decisions regarding phlebotomy. Prior to locking the database Takeda will evaluate the impact of changing laboratories on these endpoints.

b. Central laboratories perform ADA, inflammatory markers, and PK/PD assessments. Local laboratories may be able to perform some PD assessments (for example, TSAT, serum iron). Takeda will determine whether it is feasible to perform the remaining tests at outside laboratories or collect blood for submission to the central laboratory, or whether these tests will be omitted until the disaster is over.

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c. Sites should assess endpoints such as patient reported outcomes when the site determines such assessments are feasible and will yield reliable data.

d. Prior to locking the database, Takeda will address in the statistical analysis plan how protocol deviations related to the disaster will be handled for the prespecified analyses.

8. **Study Monitoring:** To ensure oversight of the trial, Takeda will implement remote monitoring at sites that do not allow on-site monitoring. The process of remote monitoring will depend on each site's record keeping systems and procedures for maintaining confidentiality.

9. **Personnel and Vendors:** Non-study personnel and vendors (, personnel or vendors not listed on FDA Form 1572 or equivalent form) may be asked to perform study procedures when study personnel or vendors are not available. Efforts will be made to determine whether non-study personnel are qualified before they perform protocol-specified tasks. Subsequently, these non-study personnel and vendors should be documented on Form 1572.

10. **Data Entry and Adverse Event Reporting:** Sites will endeavor to enter study data fully and in a timely manner. Critical data to enter are drug dosing, key laboratory parameters (for example, hematocrit) and adverse events. SAEs and all cancer events regardless of seriousness must be reported within 24 hours of the site becoming aware of the event.

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Changes in study visit schedules, missed visits, or participant discontinuations may lead to missing information (for example, for protocol-specified procedures). The reason for missing data, including the relationship to disaster for missing protocol-specified information (for example, from missed study visits) will be documented. This information will be summarized in the clinical study report. Changes to study operations and endpoints in response to a disaster or to improve participant safety are not considered violations of Good Clinical Practices.

Clinical investigators should engage with their IRB/IEC as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated. When possible, sites should obtain IRB/IEC approval before implementing any changes. Such changes to the protocol or investigational plan to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (for example, to limit exposure to COVID-19) may be implemented without IRB/IEC approval or before filing a protocol amendment but are required to be reported afterwards.

Takeda will make appropriate changes to the protocol and submit the revised protocol to the FDA and other Healthy Authorities in accordance with current regulations and guidelines.

APPENDIX 5. MYELOFIBROSIS SYMPTOM ASSESSMENT FORM VERSION 4.0 (MFSAF V4.0)

Myelofibrosis Symptom Assessment Form Version 4.0 Diary

1. During the past 24 hours, how severe was your worst fatigue (weariness, tiredness)?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 24 hours, how severe was your worst night sweats (or feeling hot or flushed)?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 24 hours, how severe was your worst itching?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 24 hours, how severe was your worst abdominal discomfort (feeling pressure or bloating)?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 24 hours, how severe was the worst pain under your ribs on your left side?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 24 hours, what was the worst feeling of fullness you had after beginning to eat?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 24 hours, how severe was your worst bone pain (not joint or arthritis pain)?	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

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Gwaltney C, Paty J, Kwitkowski VE, et al. Development of a harmonized patient-reported outcome questionnaire to assess myelofibrosis symptoms in clinical trials. Leuk Res. 2017;59:26-31. doi:10.1016/j.leukres.2017.05.012.

APPENDIX 6. MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS 10)

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS 10)

Symptom	1 to 10 (0 if absent) ranking (1 is most favorable and 10 least favorable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours.	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (As bad as you can imagine)
Circle the one number that describes how, during the PAST 24 HOURS how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100°F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

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APPENDIX 7. PROMIS® FATIGUE SHORT FORM 8A

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PROMIS® Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
HI7	I feel fatigued.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41	How run-down did you feel on average? ..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35	How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP49	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3	How often did you have to push yourself to get things done because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP16	How often did you have trouble finishing things because of your fatigue?..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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English
16 March 2020
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APPENDIX 8. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Patient Global Impression of Severity:

Please choose the response below that best describes the severity of your polycythemia vera symptoms over the past 24 hours:

✓*one box only:*

❑ 0	❑ 1	❑ 2	❑ 3
None	Mild	Moderate	Severe

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United States Food and Drug Administration. Patient-focused drug development guidance public workshop. Methods to identify what is important to patients and select, develop or modify fit-for-purpose clinical outcomes assessments, Appendix 4. Workshop Date: October 15-16, 2018. https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select.

APPENDIX 9. PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

Patient Global Impression of Change:

Please choose the response below that best describes the overall change in your **polycythemia vera symptoms** since you started taking the study medication:

✓*one box only:*

❑ 1	❑ 2	❑ 3	❑ 4	❑ 5
Much Better	A Little Better	No Change	A Little Worse	Much Worse

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United States Food and Drug Administration. Patient-focused drug development guidance public workshop. Methods to identify what is important to patients and select, develop or modify fit-for-purpose clinical outcomes assessments, Appendix 4. Workshop Date: October 15-16, 2018. https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select

APPENDIX 10. EUROPEAN ORGANIZATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ-C30)

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋
Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

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Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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