Rusfertide in PV (REVIVE) – Late Breaker Oral Presentation June 11, 2023

TARGETED THERAPY OF UNCONTROLLED ERYTHROCYTOSIS IN POLYCYTHEMIA VERA WITH THE HEPCIDIN MIMETIC, RUSFERTIDE: BLINDED RANDOMIZED WITHDRAWAL RESULTS OF THE REVIVE STUDY

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June 11, 2023
Late Breaker Oral Presentation

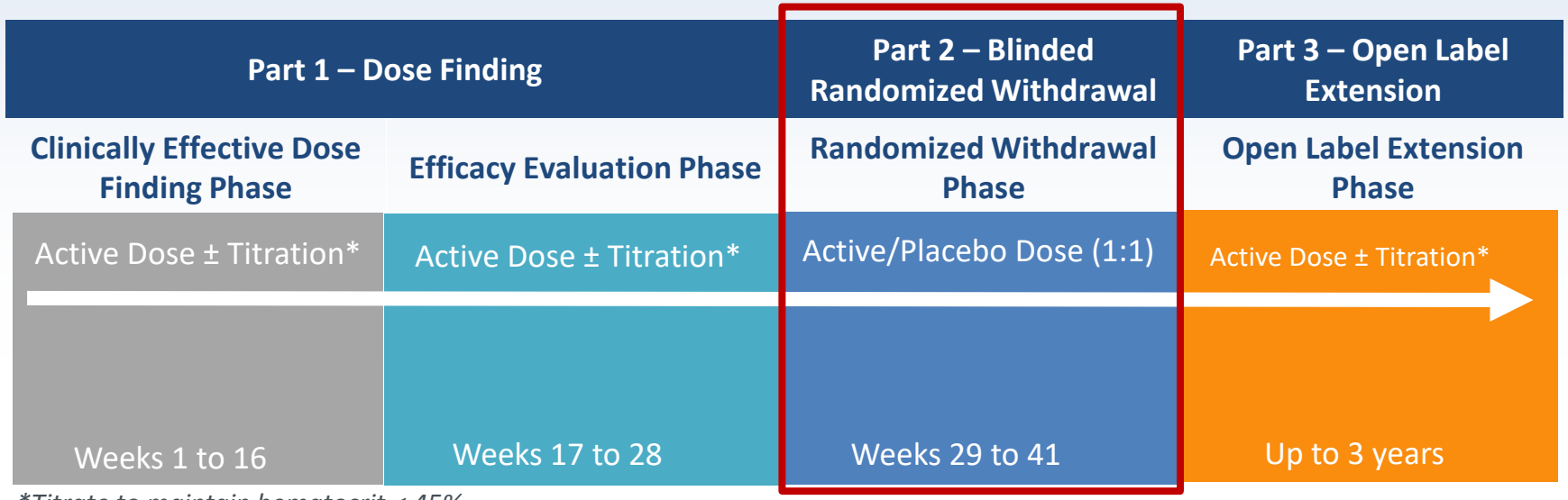
DISCLOSURES

Protagonist Therapeutics, Inc (Advisory board)
Protagonist Therapeutics, Inc (Honoraria)

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

GOAL: Maintain Hematocrit <45%

Clinical Proof-of-Concept Study with Add-On Rusfertide



**Titrate to maintain hematocrit < 45%*

STUDY ELIGIBILITY:

- Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria
- ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
- Rusfertide (PTG-300) doses of 10-120 mg administered subcutaneously weekly added to prior standard therapy
- All patients prior to first rusfertide dose were phlebotomized to HCT <45% to standardize the starting HCT

KEY ENDPOINTS:

- Safety

Part 1

- Number and rate of phlebotomies compared to historic experience

Part 2

- Proportion of Responders
  - Maintain Hematocrit <45%
  - Reduction in Phlebotomies
- Patient Outcomes: MPN-SAF TSS

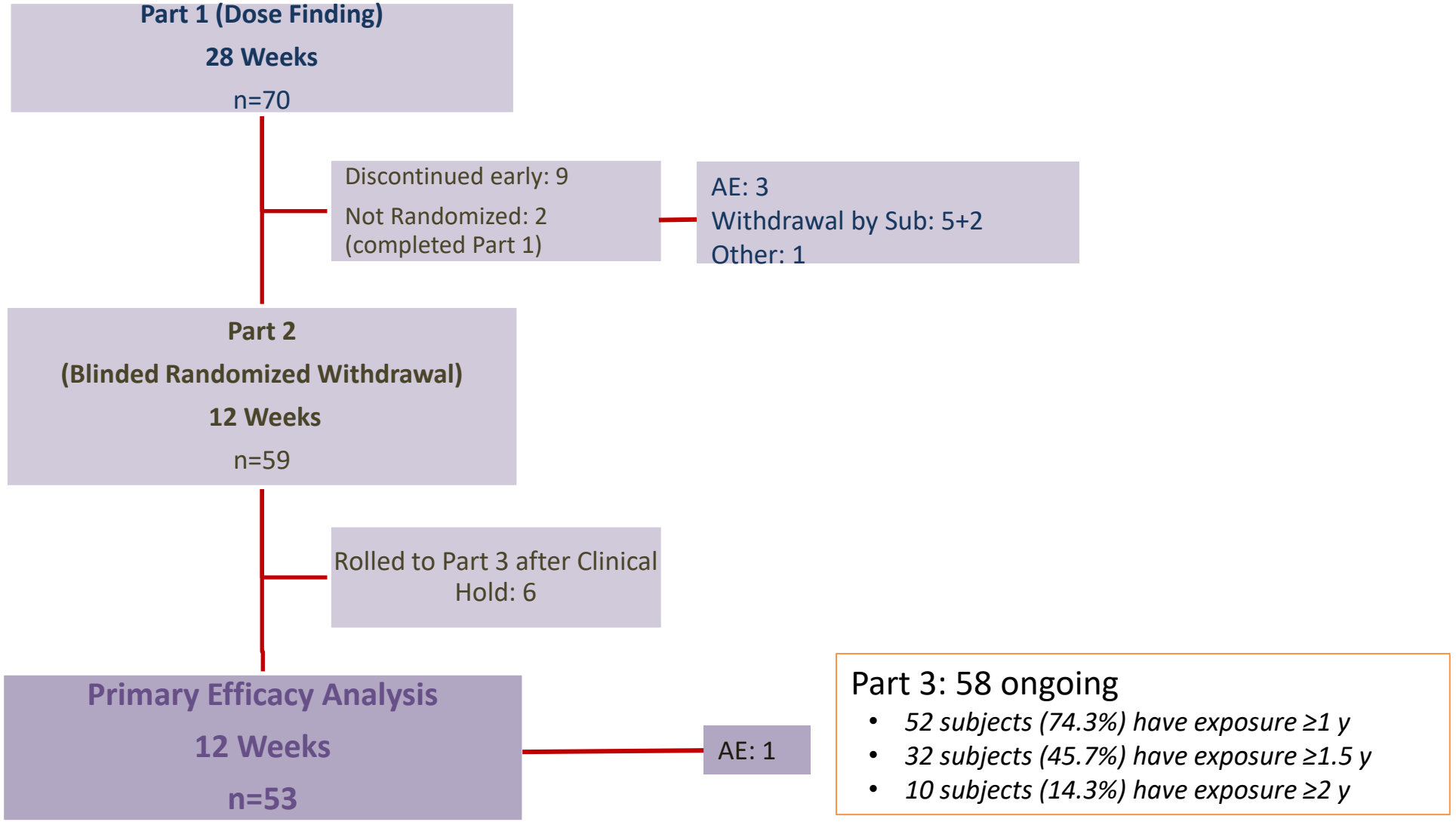
PURPOSE OF RESEARCH

- Polycythemia Vera is a myeloproliferative neoplasm characterized by excessive production of red blood cells (RBCs)[1].
- Elevated hematocrit (HCT) is a hallmark of the disease, indicating overproduction of RBCs[2].
- Uncontrolled HCT is associated with higher rates of death from cardiovascular causes or thrombotic events[3].
- Maintaining HCT<45% is critical in PV, as per NCCN and ELN guidelines to decrease the risk of TE and CV events.
- Current standard of care does not maintain HCT <45% in a majority of patients[4,5].
- Hepcidin is a peptide hormone that is the body's main regulator of iron homeostasis and controls the availability of iron for formation of red blood cells.
- Rusfertide is a novel hepcidin mimetic that is designed to maintain iron homeostasis and normalize erythrocytosis.
- The REVIVE Phase 2 study evaluated the safety and efficacy of rusfertide in patients with polycythemia vera (PV) who had a high phlebotomy burden with current standard of care.

1. NORD Rare Disease Database, Polycythemia Vera. https://rarediseases.org/rare-diseases/polycythemia-vera/. **2.** Spivak. Ann Hematol 2018; 19(2):1-14. **3.** Marchioli et al. N Engl J Med 2013; 368:22-33 **4.** Verstovsek et al. Ann Hematol. 2023; 102:571-581 **5.** Chornenki et al. Leuk Res. 2018 Jul;70:62-66

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

Disposition



Part 3: 58 ongoing

- *52 subjects (74.3%) have exposure ≥1 y*
- *32 subjects (45.7%) have exposure ≥1.5 y*
- *10 subjects (14.3%) have exposure ≥2 y*

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

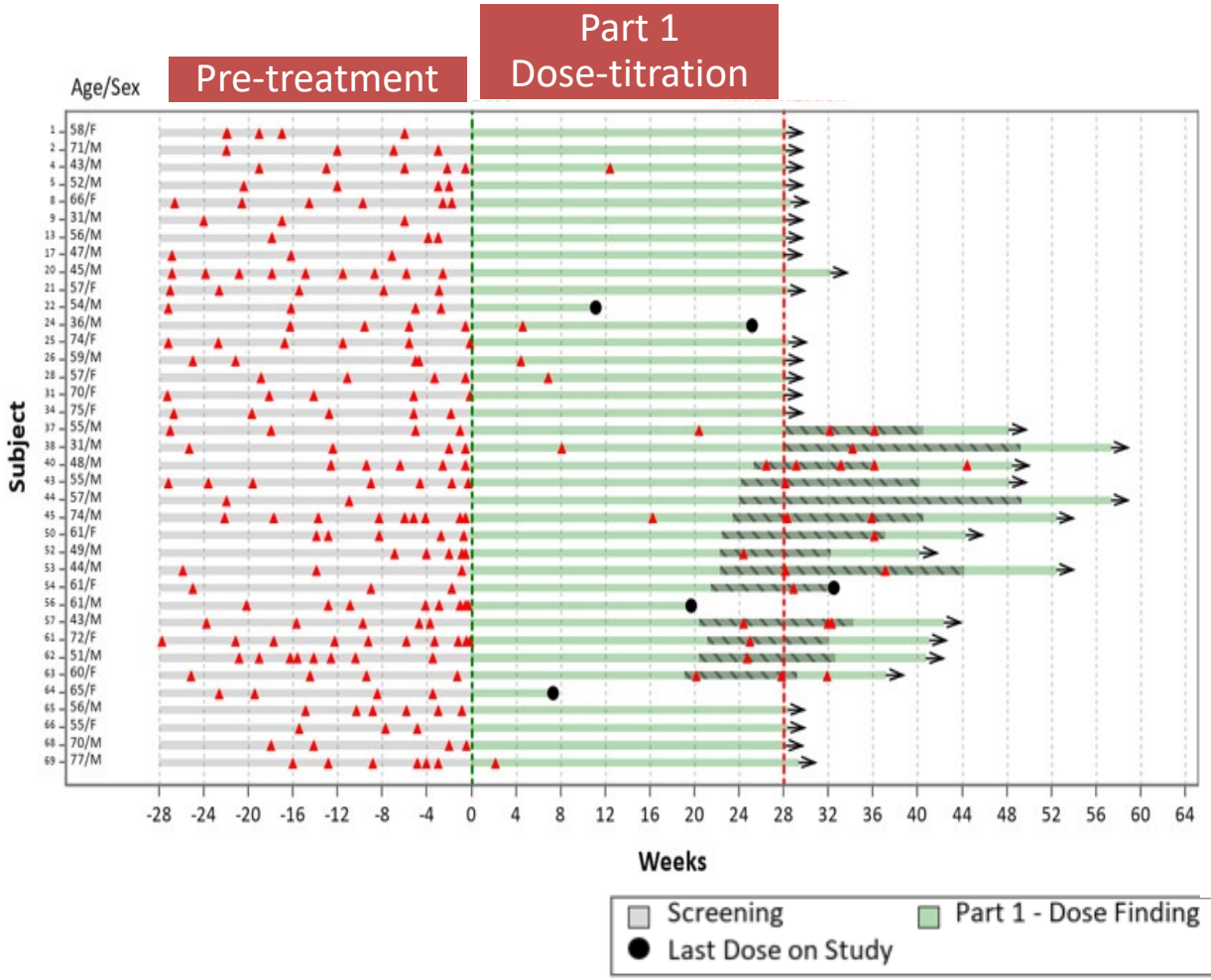
Baseline Demographics and Disease Characteristics

		Randomized Part 2 (N=53)	
	Part 1 (N=70)	Placebo (N=27)	Rusfertide (N=26)
Age, y	57.3±12.19	60.7±11.18	54.9±12.45
Gender			
Male	49 (70%)	17 (63%)	21 (80.8%)
Female	21 (30%)	10 (37%)	5 (19.2%)
BMI, kg/m2	29.6±5.36	30.1±5.76	28.7±4.55
Disease Characteristics			
Age at Diagnosis, y	52.3±13.49	55.9±12.15	50.3±11.75
PV Duration, y	5.1±6.21	5.0±4.77	4.6±5.70
Risk			
High Risk	39 (55.7%)	17 (63%)	11 (42.3%)
Low Risk	31 (44.3%)	10 (37%)	15 (57.7%)
Cytoreductive Therapy	33 (47.1%)	16 (59.3%)	8 (30.8%)
Hydroxyurea	18 (25.7%)	9 (33.3%)	4 (15.4%)
Interferon	9 (12.9%)	5 (18.5%)	2 (7.7%)
JAK inhibitor	5 (7.1%)	2 (7.4%)	2 (7.7%)

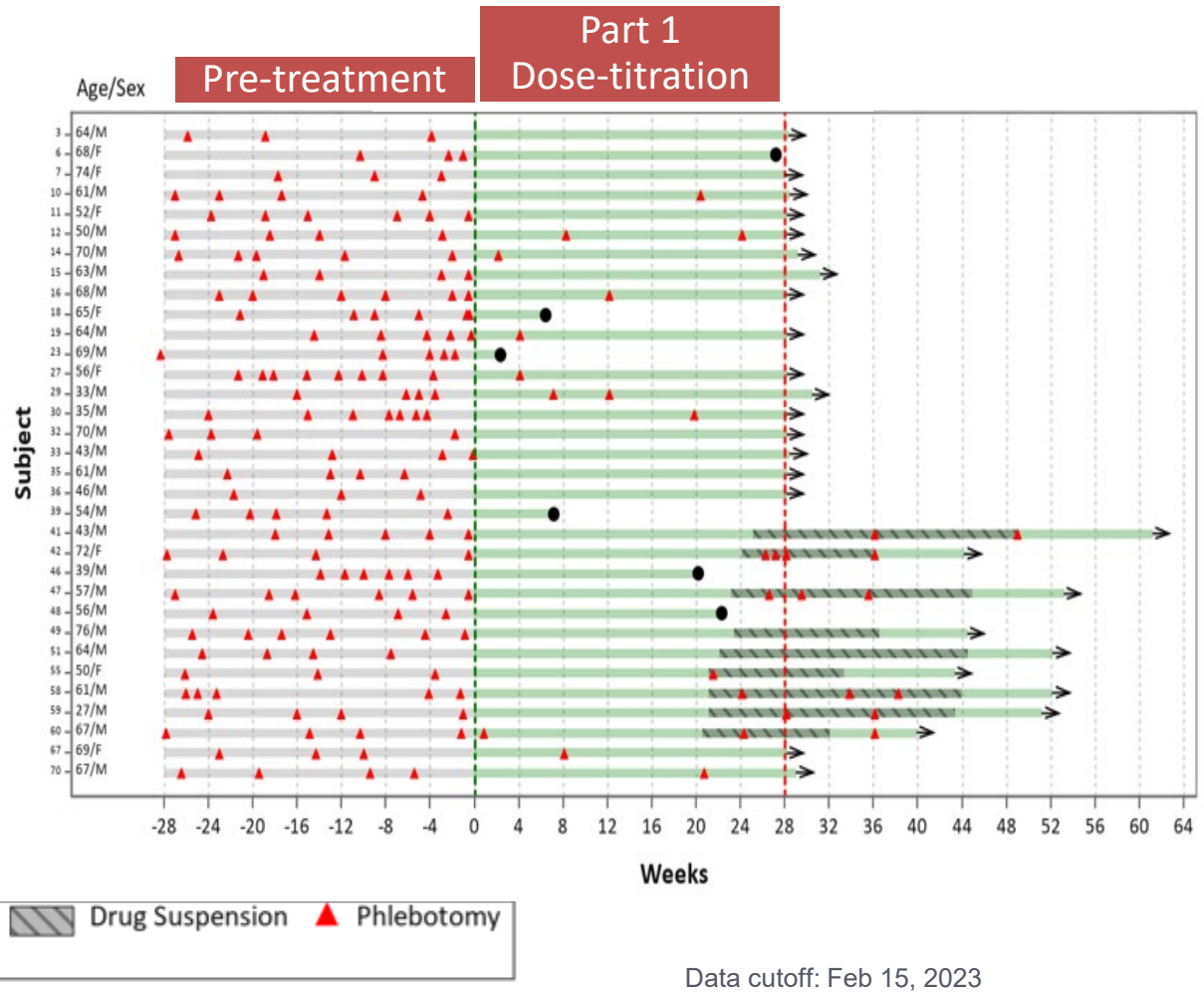
REVIVE Study: Efficacy

Meaningful Reduction in Phlebotomy Frequency Following Rusfertide Administration

Phlebotomy Only (n=37)



Phlebotomy and Cytoreductives (n=33)



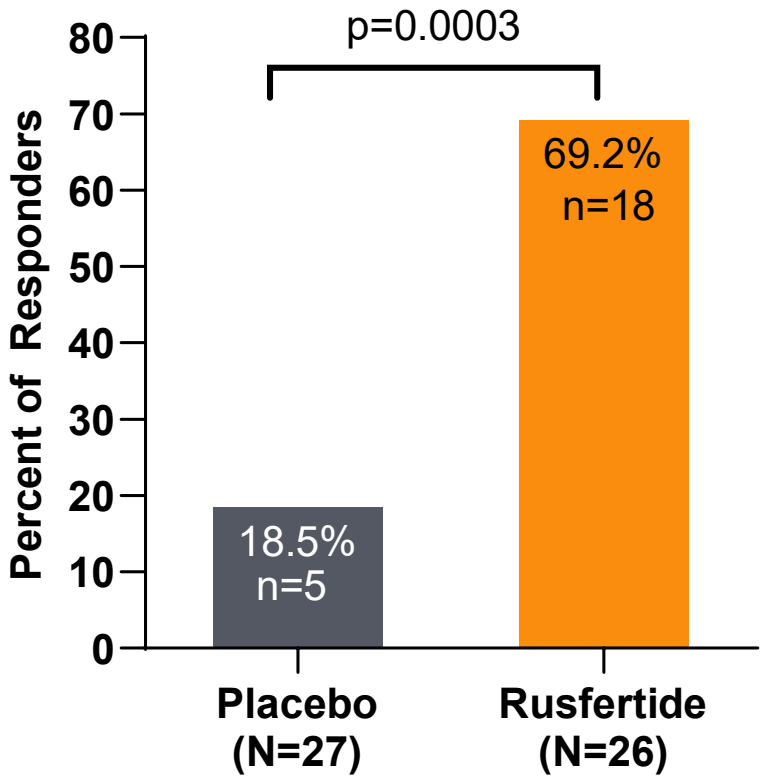
Screening | Part 1 - Dose Finding | Drug Suspension | Phlebotomy | Last Dose on Study

Data cutoff: Feb 15, 2023

REVIVE Study: Part 2, Blinded Randomized Withdrawal, Weeks 29-41

Rusfertide Met the Primary Endpoint of Efficacy

Highly significant Efficacy*
in rusfertide arm vs. placebo



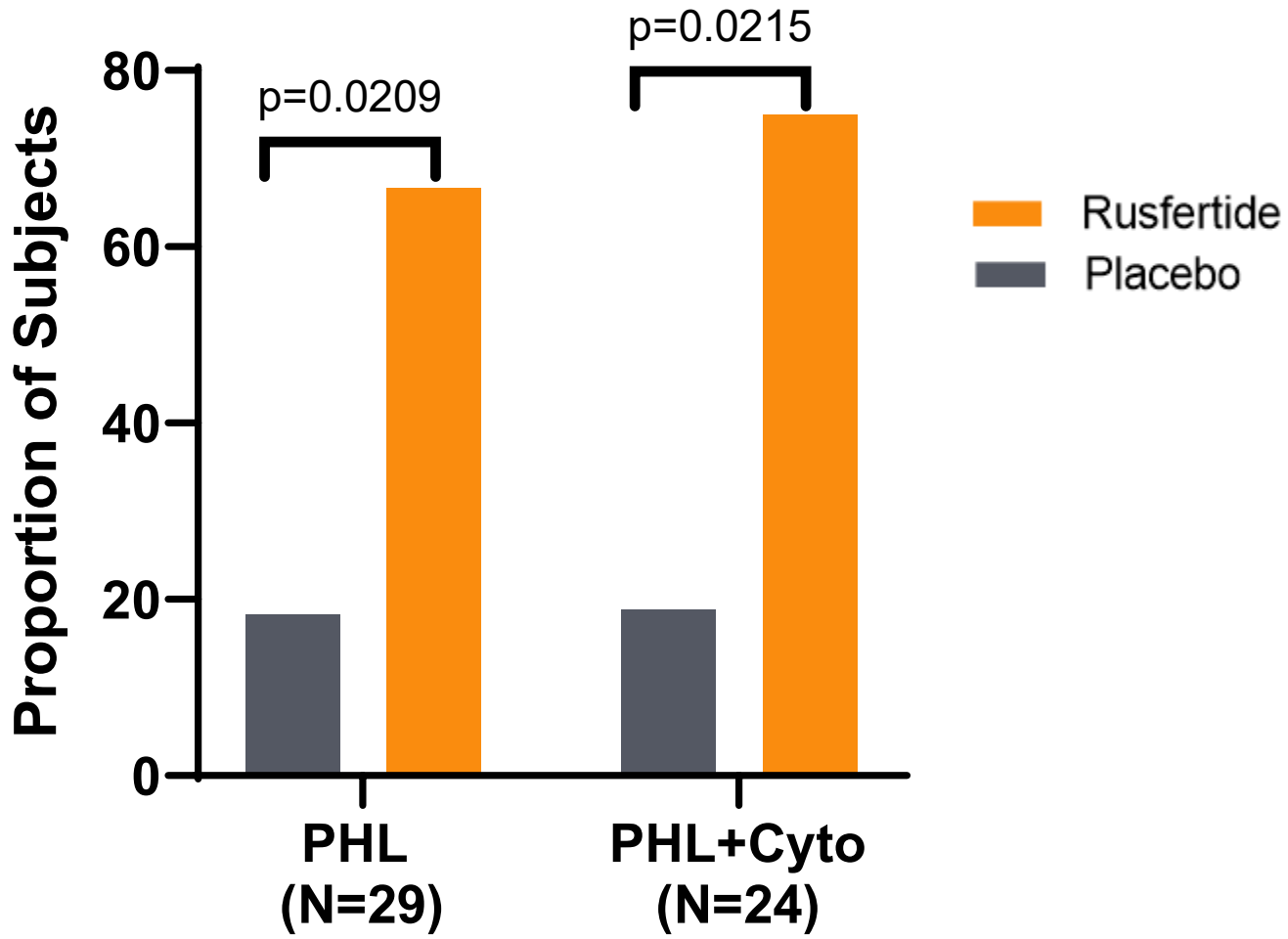
- **69.2% subjects** (18 out of 26) are responders. 8 non-responders as per protocol definition
  - 3 fulfilled the phlebotomy eligibility criteria
  - 5 discontinued treatment per patient/investigator discretion
- All 8 non-responders continued in part 3 open label extension of the study
  - 7 out of 8 are currently continuing treatment
- **92.3% subjects** (24 out of 26) in rusfertide arm did not receive phlebotomy in part 2, 12-week randomization part of the study

**Responder definition as per protocol*

- *Did not receive a phlebotomy*
- *Completed 12 weeks of treatment*
- *Hematocrit control maintained without phlebotomy eligibility, which is defined as*
  - *Hematocrit ≥45% that was ≥3% higher than Week 29 pre-randomization hematocrit value* ***or***
  - *Hematocrit >48%* ***or***
  - *An increase of ≥5% in hematocrit compared to Week 29 pre-randomization hematocrit value*

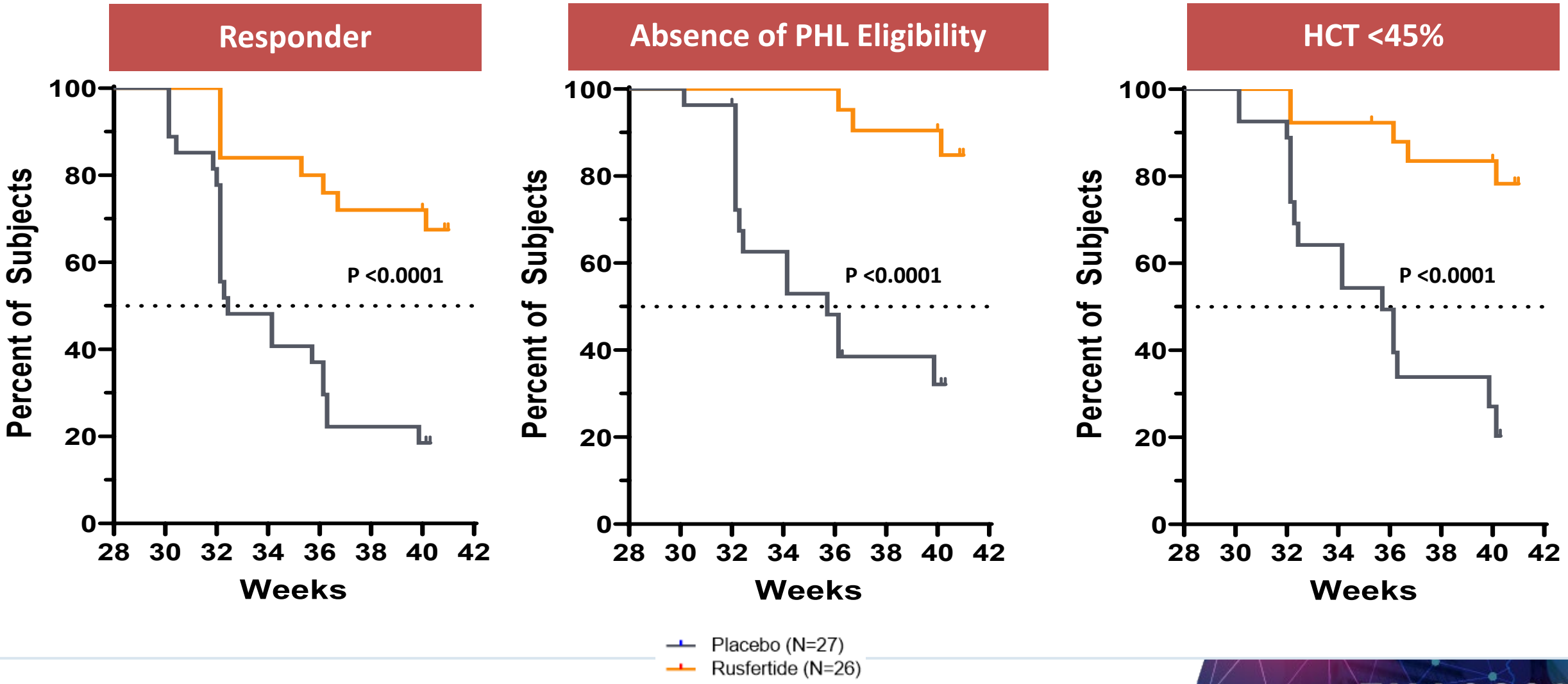
REVIVE Study: Efficacy

Efficacy over Placebo Demonstrated in Phlebotomy Alone and Phlebotomy + Cytoreductive Subgroups



REVIVE Study: Consistent Efficacy

Rusfertide Significantly Delays Time to Treatment Failure on Multiple Outcomes Compared to Placebo

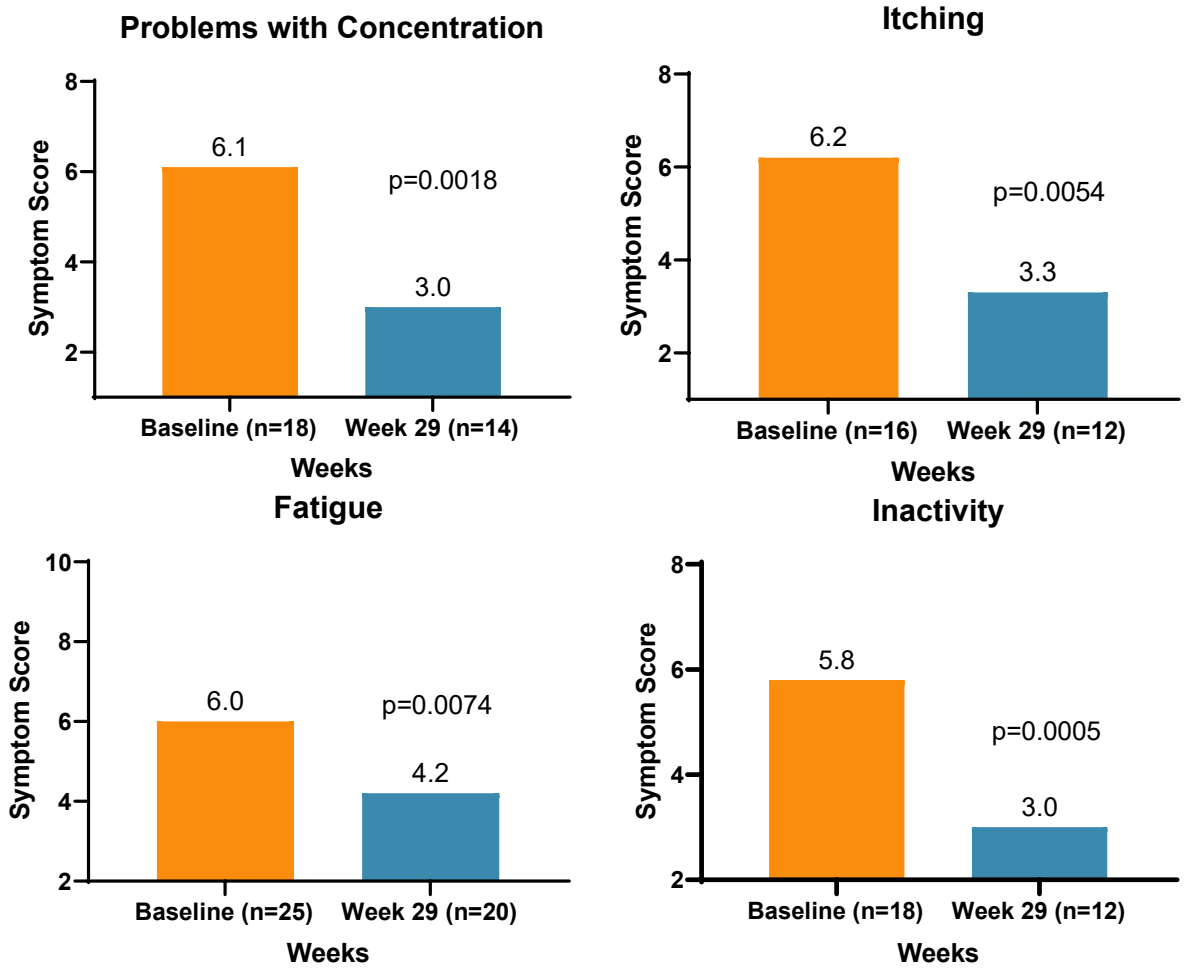


REVIVE Study: PV Symptoms in Part 1

Improvement in Patients Experiencing Moderate or Severe Symptoms at Baseline

- Part 1 is an open-label 28-week treatment with rusfertide that allows evaluation of symptom improvement

Symptom Improvement in Part 1*



*In Part 2, subjects randomized to Placebo treatment do not remain on treatment for long (median 4.4 weeks), so it is not possible to compare effects on symptoms.

Individual symptoms assessed using MPN-SAF
p-value are based on paired comparisons

REVIVE Study – Safety and Exposure

Rusfertide was Generally Well Tolerated

TEAEs by Preferred Term Noted at ≥15%	N=70
Subjects with at least one TEAE	70 (100%)
Injection site erythema	45 (64.3)
Injection site pain	29 (41.4)
Injection site pruritus	28 (40.0)
Fatigue	22 (31.4)
Injection site mass	18 (25.7)
Pruritus	18 (25.7)
Arthralgia	17 (24.3)
Injection site swelling	17 (24.3)
Dizziness	16 (22.9)
Headache	16 (22.9)
Nausea	16 (22.9)
Anemia	14 (20.0)
COVID-19	14 (20.0)
Injection site irritation	13 (18.6)
Injection site bruising	11 (15.7)

- 70 subjects were enrolled in the rusfertide REVIVE study
  - 52 subjects (74.3%) have exposure ≥1 y
  - 32 subjects (45.7%) have exposure ≥1.5 y
  - 10 subjects (14.3%) have exposure ≥2 y
- Rusfertide was generally well tolerated
  - A majority (83%) of TEAEs were Grade 1 or 2
    - 17% subjects reported Grade 3 TEAEs
    - There were no Grade 4 or 5 TEAEs
  - Most common TEAEs were injection site reactions (ISR)
    - Events were localized, Grade 1 or 2 in severity, and generally did not lead to treatment discontinuation
    - ISRs decreased in incidence with continued treatment
  - Symptoms associated with PV such as fatigue, pruritus, headache and dizziness were the second most common reported AEs
  - Two events related to treatment with rusfertide led to discontinuation (mild thrombocytosis and recurrent grade 1 injection site erythema)

Data as of 15 February 2023

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

Overall Summary

- Rusfertide is a first-in-class hepcidin mimetic that selectively targets uncontrolled erythrocytosis.
- The REVIVE study demonstrated a significantly higher efficacy with rusfertide compared to placebo in subjects with PV.
- The study met the efficacy endpoints (Proportion of Responders, Absence of phlebotomy eligibility, Hematocrit control).
- Rusfertide demonstrated favorable effects on several Patient-Reported Outcomes (fatigue, problems with concentration, pruritus, inactivity), particularly in patients who were burdened by these symptoms.
- Rusfertide was generally well tolerated. TEAEs were generally Grade 1 or 2. The most common TEAEs was ISRs. There were no Grade 4 or 5 TEAEs.
- Current standard of care therapy in PV does not consistency maintain hematocrit <45%, thereby increasing the risk of thromboembolic events. Rusfertide has the potential to consistently maintain hematocrit <45%.
- Rusfertide is currently being investigated in the ongoing placebo-controlled VERIFY Phase 3 study.

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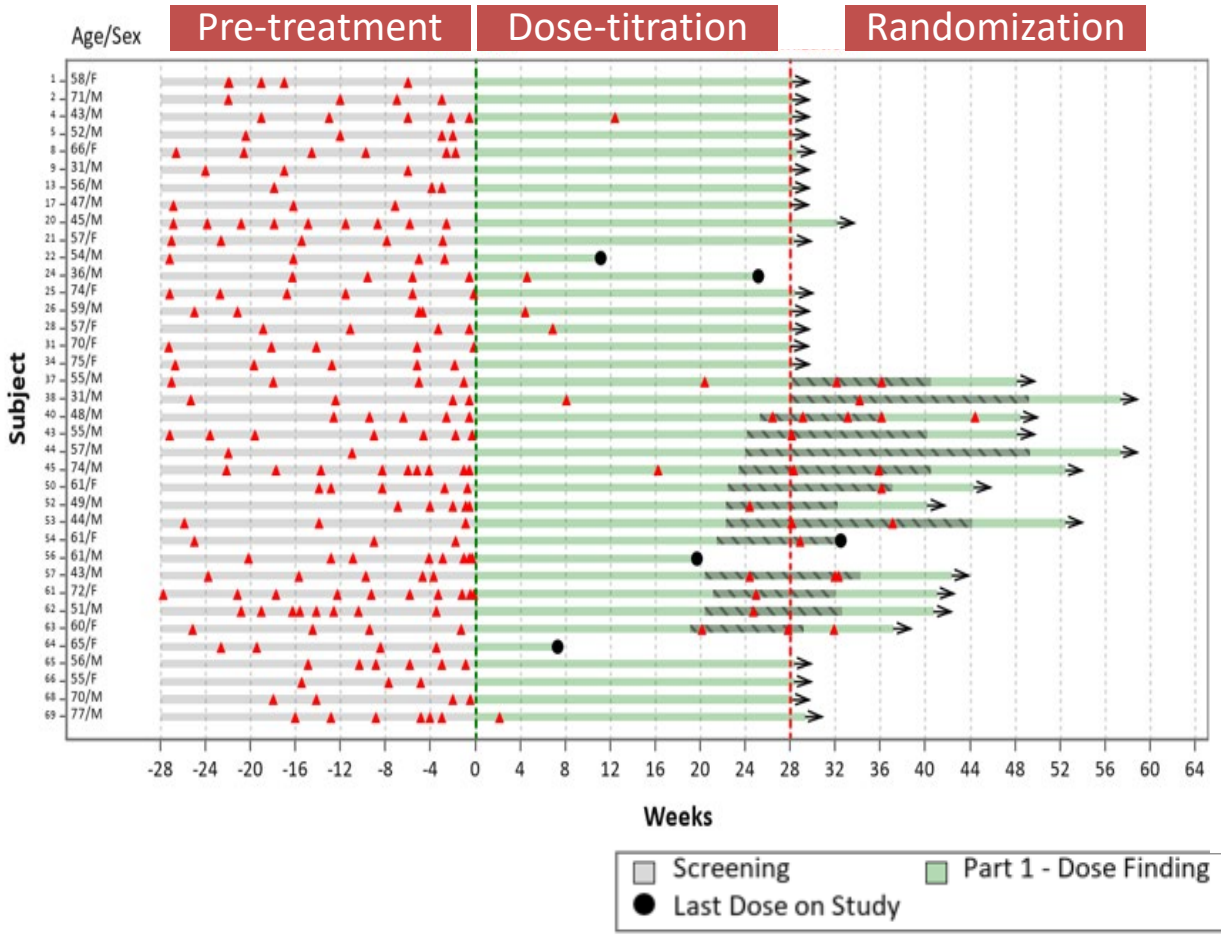

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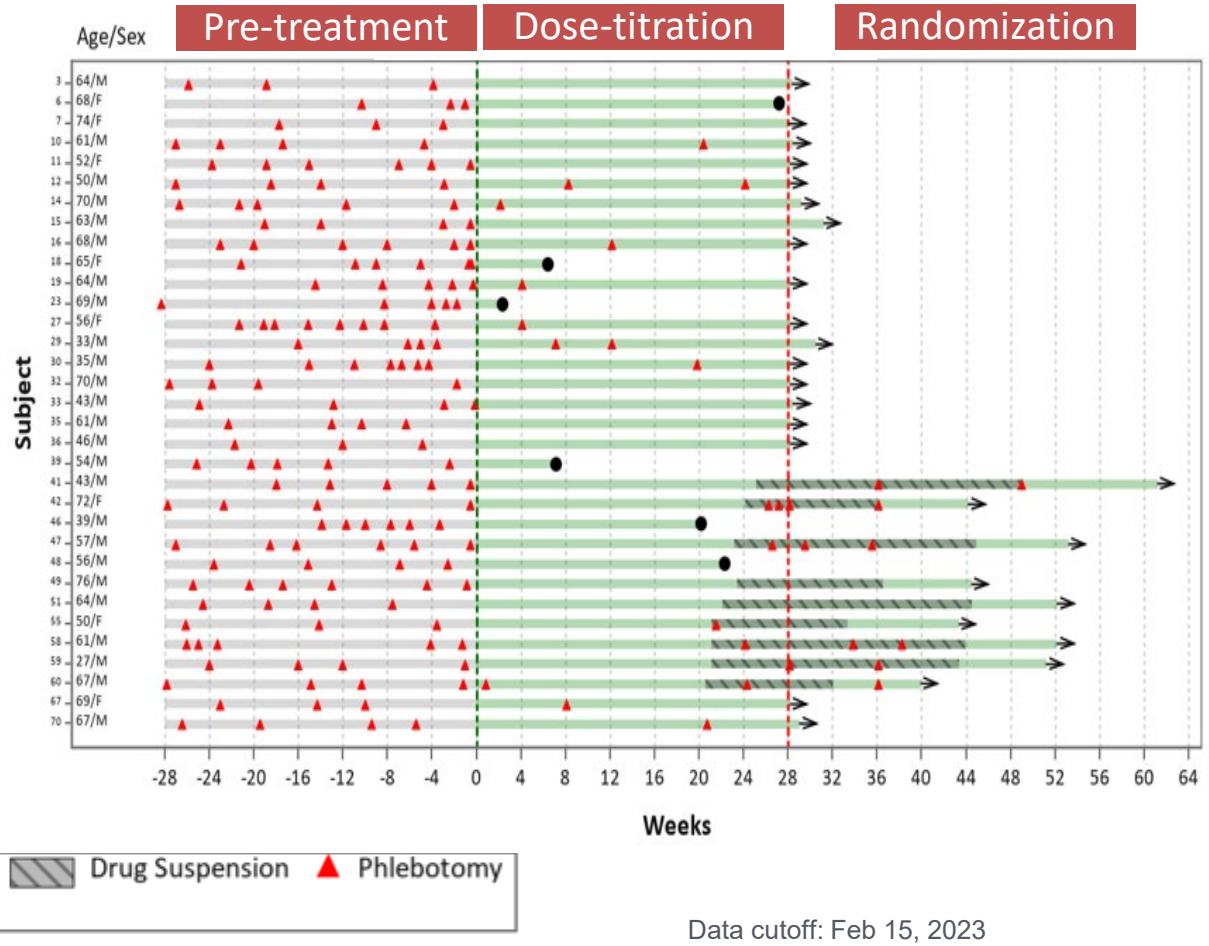

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