Protagonist Therapeutics

COMPANY OVERVIEW

Dinesh V. Patel, Ph.D.
President & CEO

July 4, 2023

Forward-looking Statements

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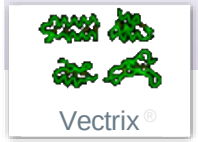
Peptide-based Medicines

Potency

1 Computational
Vectrix, Clusters


Vectrix®


Clusters

2 Phage Libraries
Hits

3 Peptide Chemistry
SAR, Leads

Stability

4 Oral Stability
Peptidomimetics
GI Assays

2 GI-Restricted
Targeted GI
absorption & delivery

3 Systemic Availability
Formulation
SAR, Transport

Rusfertide - Ph3

JNJ-2113 – Ph2b (formerly PN-235)

Heme Franchise

Oral Peptides

Discovery & pre-clinical development against new targets in hematology and immunology

Protagonist Therapeutics

Ongoing Ph3 Study of Rusfertide in PV | Collaboration with Janssen Toward Oral IL-23R Antagonist

- **Rusfertide**
  - Injectable hepcidin hormone mimetic
  - **VERIFY: Ph3 study in polycythemia vera (PV)**
  - **REVIVE: Ph2 PV study with randomized withdrawal****
  - **PACIFIC: Ph2 high HCT PV study****
  - Orphan and Fast Track status
  - Multi-billion-dollar gross sales potential in hematological diseases
  - Fully owned asset

- **JNJ-2113* (formerly PN-235)**
  - Collaboration with **Janssen**
  - **Oral IL-23R antagonist**
  - Multiple clinical studies
    - **FRONTIER 1: Ph2b study in psoriasis****
    - FRONTIER 2: Extension of FRONTIER 1
    - **SUMMIT: Ph2a study in psoriasis****
    - Multiple Phase 1 studies**
  - New planned studies
    - Phase 3 study in psoriasis
    - Phase 2b study in ulcerative colitis

Strong cash position, with cash runway through the end of 2025

*Also known as JNJ-77242113 **Completed

Discovery, Pre-Clinical & Clinical Development

Ongoing Projects and Future Plans

- Primary focus on completing Phase 3 VERIFY study of Rusfertide in polycythemia vera

- Separate 2-year extension (PTG-300-21) study will open this year for patients who have completed participation in the REVIVE study
  - Total duration of treatment up to 5 years

- Discovery projects in progress
  - Oral hepcidin
  - New targets in hematology
  - New targets in immunology focused on ‘oral peptide approach’ as a strong differentiator

Product Portfolio

Addressing Unmet Needs in Multiple Indications with Multi-Billion Dollar Market Potential

Programs	Discovery/ Pre-Clinical	Phase 1	Phase 2	Phase 3	Key Milestones

HEMATOLOGY & BLOOD DISORDERS

Hepcidin Mimetic **Rusfertide (PTG-300)**

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POLYCYTHEMIA VERA (PV)

- Ph3 VERIFY *
  - VERIFY: ~250 patient, double-blind, placebo-controlled, Enrollment completion 1Q 24
- Ph2 REVIVE
  - REVIVE: 70 patient randomized withdrawal completed, OLE ongoing
- Ph2 elevated HcT (>48%) PACIFIC
  - PACIFIC: 52-wk open-label study completed

Undisclosed Target

- Hematology *
  - Discovery hits/leads

INFLAMMATORY & IMMUNOMODULATORY DISEASES

Undisclosed Target

- Immunology *
  - Discovery hits/leads

Oral IL-23R Antagonist (Partnered) **JNJ-2113 (PN-235)**

janssen

PSORIASIS

- Ph2b FRONTIER-1 & -2
- Ph3 trial (planned) *
  - FRONTIER 1 & 2: 255-patient psoriasis study completed, LTE Ongoing
  - Psoriasis Ph3: Study initiation planned
- Ph2a SUMMIT
  - SUMMIT: 90 patient psoriasis delayed release formulation study completed

ULCERATIVE COLITIS (UC)

- UC Ph2b trial (planned) *
  - UC Ph2b: Study initiation planned 4Q 23

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* *New Information*

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Rusfertide (PTG-300): Hepcidin Mimetic

Addressing Unmet Needs in Polycythemia Vera

Rusfertide

Building a Heme Franchise

Polycythemia Vera

- Efficacy
- Durability of Response
- QoL – Symptom Improvement
- Safety
- New studies in PV

Hereditary Hemochromatosis

- Positive clinical PoC

Potential Indications Under Review

- Sickle cell disease
- Porphyria
- Erythrocytosis

Polycythemia Vera

Disease Background

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]

Serious, chronic disease associated with increased thrombotic and cardiovascular risks[1,2]

Rare disease with ~100,000 diagnosed patients in US[1]

- Diagnosed commonly in individuals 50-70 years of age
- Median survival ~20 years

Treatment goal is to control

HCT<45%

to minimize TEs, CV events, and death[3]

1. NORD Rare Disease Database, Polycythemia Vera. https://rarediseases.org/rare-diseases/polycythemia-vera/. **2.** Spivak JL. Ann Hematol 2018; 19(2):1-14. **3.** Marchioli R, et al. N Engl J Med 2013; 368:22-33

Polycythemia Vera

A Blood Disorder with Significant Unmet Needs with Current SOC[4]

1. **Maintaining HCT<45% is critical in PV, as per NCCN guidelines**

2. **Uncontrolled HCT is associated with higher rates of death from cardiovascular causes or thrombotic events[1]**
   - Burdensome symptoms including fatigue and concentration problems[2]
     - **84%** of patients report fatigue, and **23%** report spending full days in bed because of symptoms[3]
   - Impacts patient reported activities of daily living and reduce productivity[2]

3. **Real world data shows that up to 78% of patients have uncontrolled HCT with tests ≥45%[4]**
   - Current standard of care (SOC) approaches are inadequate for HCT control and symptoms management[5]

4. **There is no available pharmaceutical option with RBC-specific mechanism to target HCT**
   - Rusfertide is a mimetic of Hepcidin, the natural hormone regulating iron homeostasis and erythrocytosis

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1. Marchioli R, et al. N Engl J Med 2013; 368:22-33. **2.** Mesa R, et al. BMC Cancer. 2016;16,167. **3.** MPN Landmark Survey, PV Report (2017). **4.** Verstovsek S,, et al. Real-world treatments and thrombotic events in polycythemia vera patients in the USA. Ann Hematol. 2023 Mar;102(3):571-581. doi: 10.1007/s00277-023-05089-6. Epub 2023 Jan 13. PMID: 36637474; PMCID: PMC9977710.

Current Treatment Options for PV and Potential Limitations

Cytoreductive Therapies May Lead to Intolerance and/or Inadequate Hematocrit Control

Hydroxyurea
Hydrea®

Typically used as a first-line treatment in high-risk patients

Patients still experience periods where HCT **≥45%**,[1] potentially resulting in dose increases and in need for phlebotomies

Often discontinued due to blood counts, AEs, disease progression, or poor adherence[2]

Risk of skin cancer[3]

25% of patients become resistant or intolerant[2,4]

Interferon
Pegasys®, Besremi®

Interferons have long been used off-label in treatment; Besremi is the first interferon product approved for PV[5]

Slow onset of action, with a median time to response of **1.2 to 1.4 years**[6]

Failed to show noninferiority to HU at 12 months in the PROUD-PV study[7]

Black box warning for serious neuropsychiatric, autoimmune, ischemic, and infectious disorders[6]

Ruxolitinib
Jakafi®

Only approved for hydroxyurea-resistant or intolerant patients[7]

Improves splenomegaly, a potential marker of disease progression[8]

Potential serious side effects include thrombocytopenia, neutropenia, and anemia[7]

Risk of skin cancer[7]

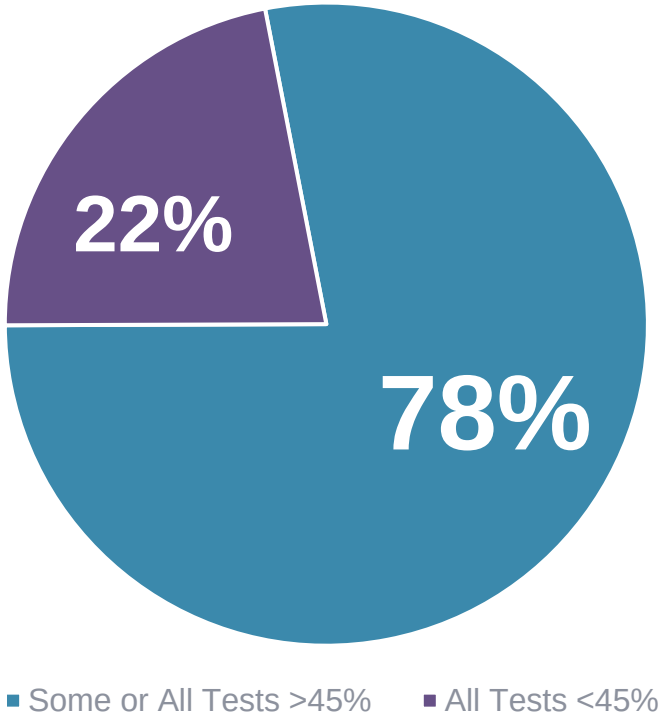
23% of patients were found to have discontinued ruxolitinib within a mean of **2 years** post treatment initiation[9]

1. Chornenki NLJ, et al. Leuk Res. 2018 Jul;70:62-66. **2.** Parasuraman S, et. al. Exp Hematol Oncol. 2016;5:3 **3.** Hydrea FDA label. **4.** Altomare I, et. al. Clin Lymphoma Myeloma Leuk. 2021;21(11):e915-e921. **4**. Gilreath JA, et. al. Blood. 2018;132 (Supplement 1). **5**. Besremi FDA label. **6**. Gisslinger H, et. al. Lancet Haematol. 2020;7(3):e196-e208. **7.** Jakafi FDA label. **8.** Coltoff R, et. al. Clin Lymphoma Myeloma Leuk. 2020;20(10): 697-703. **9.** Tremblay, D. Leuk Res. 2021;109.

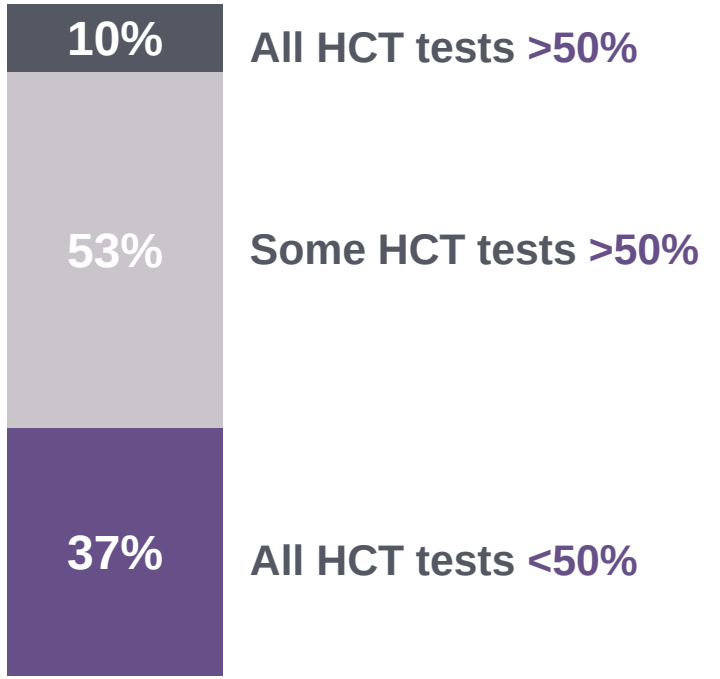
Only 22% of PV Patients Have Consistently Controlled Hematocrit

HCT is Not Managed to Guidelines, Regardless of Patients' Risk Status

All HCT tests <45%



Of the 78% of uncontrolled patients…



Uncontrolled HCT >45% leads to a greater risk of thrombotic events, cardiovascular events, death, and may impact QoL[2]

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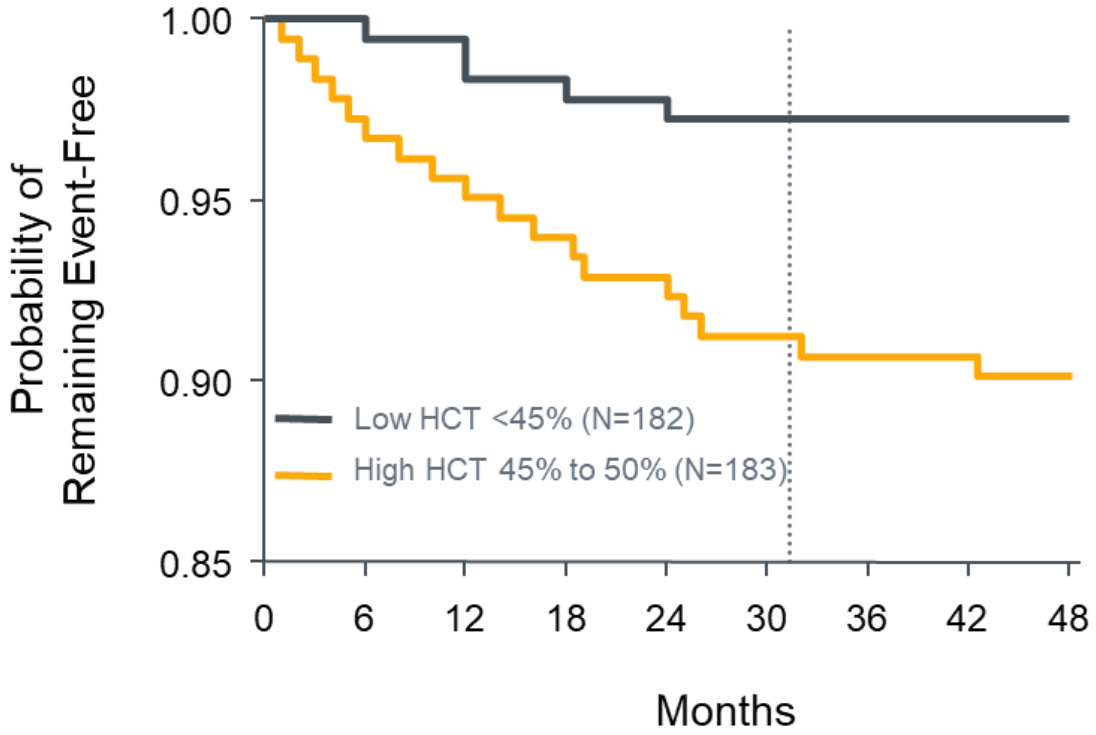
Analysis of real-world Symphony data from 2018-2019, including 4,264 PV patients with ≥2 HCT tests following Tx initiation. Verstovsek S, et al. Blood. 2020 Nov; 136:1-2 supplement 1 (abstract published, manuscript accepted for publication) **2.** Marchioli R, et al. N Engl J Med 2013; 368:22-33. doi:10.1056/NEJMoa1208500.

Increased Hematocrit Is Associated with Increased Morbidity and Mortality

Current Treatment Options Are Inadequate

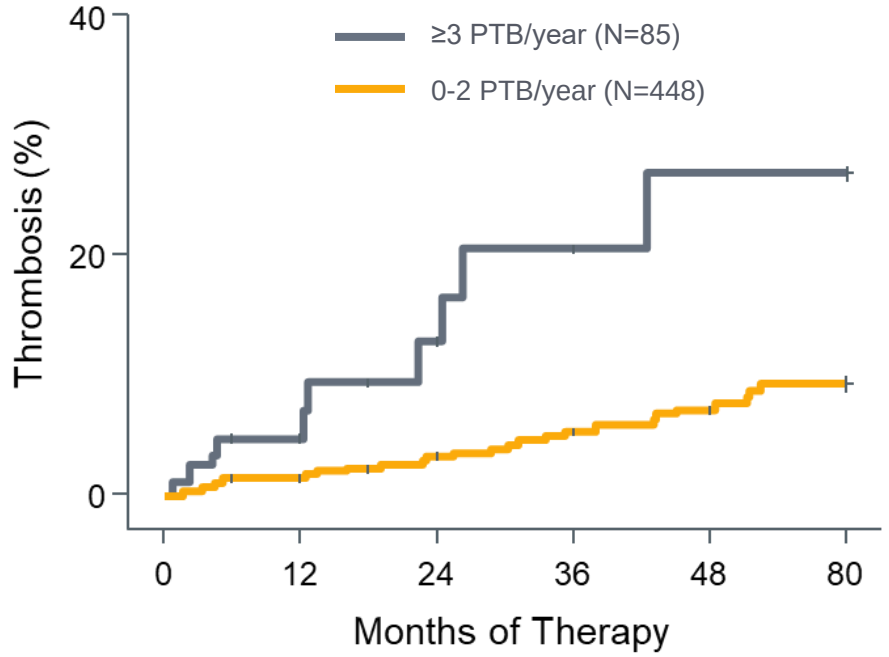
Elevated Hematocrit Contributes to ~4x Increased Risk of CV Death and Major Thrombosis



Marchioli, R. et al., N Engl J Med. 2013

Phlebotomy, Even with Concomitant Cytoreductive Therapy, Is Inadequate in Reducing Thrombotic Risk

All HU-treated (*P<0.0001*)



Alberto Alvarez-Larran et al. Haematologica 2017; 102:103-109

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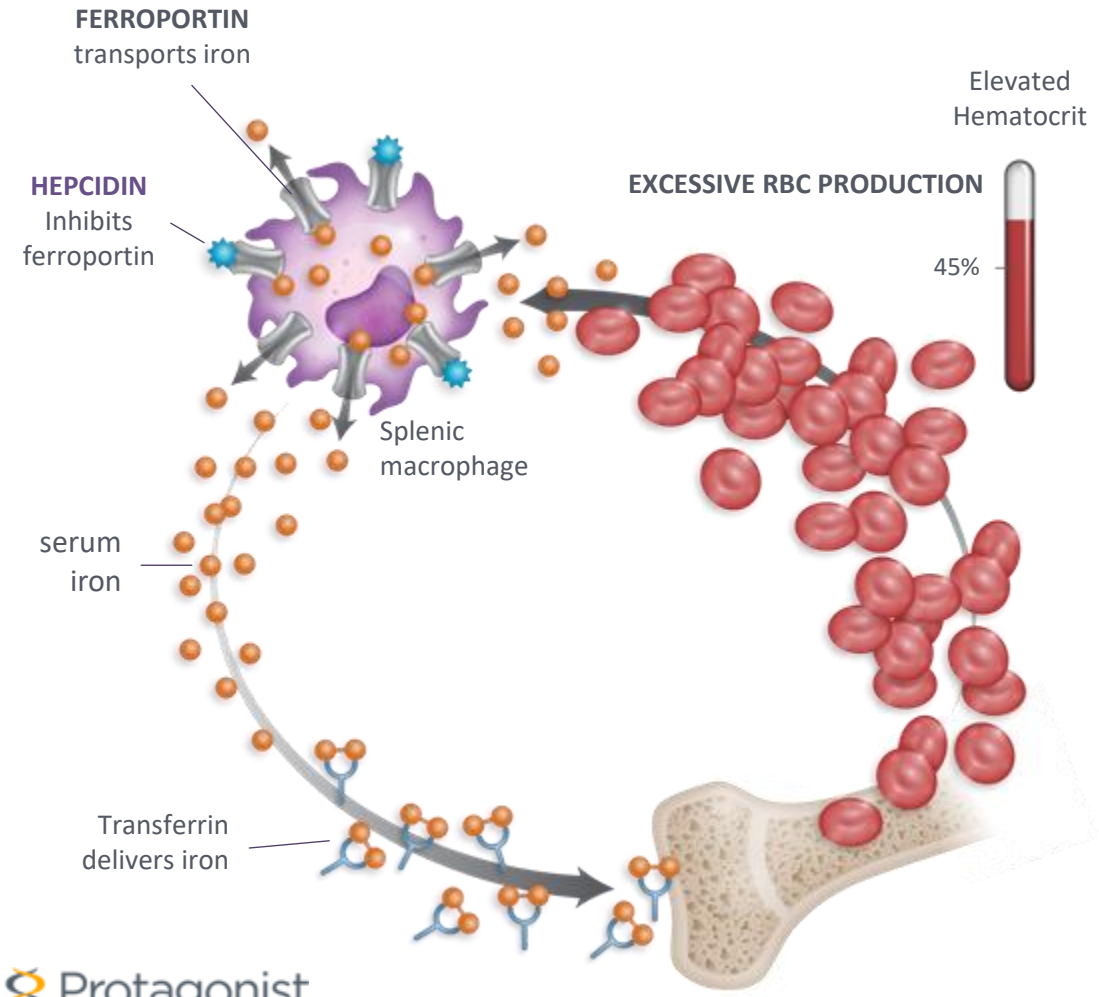
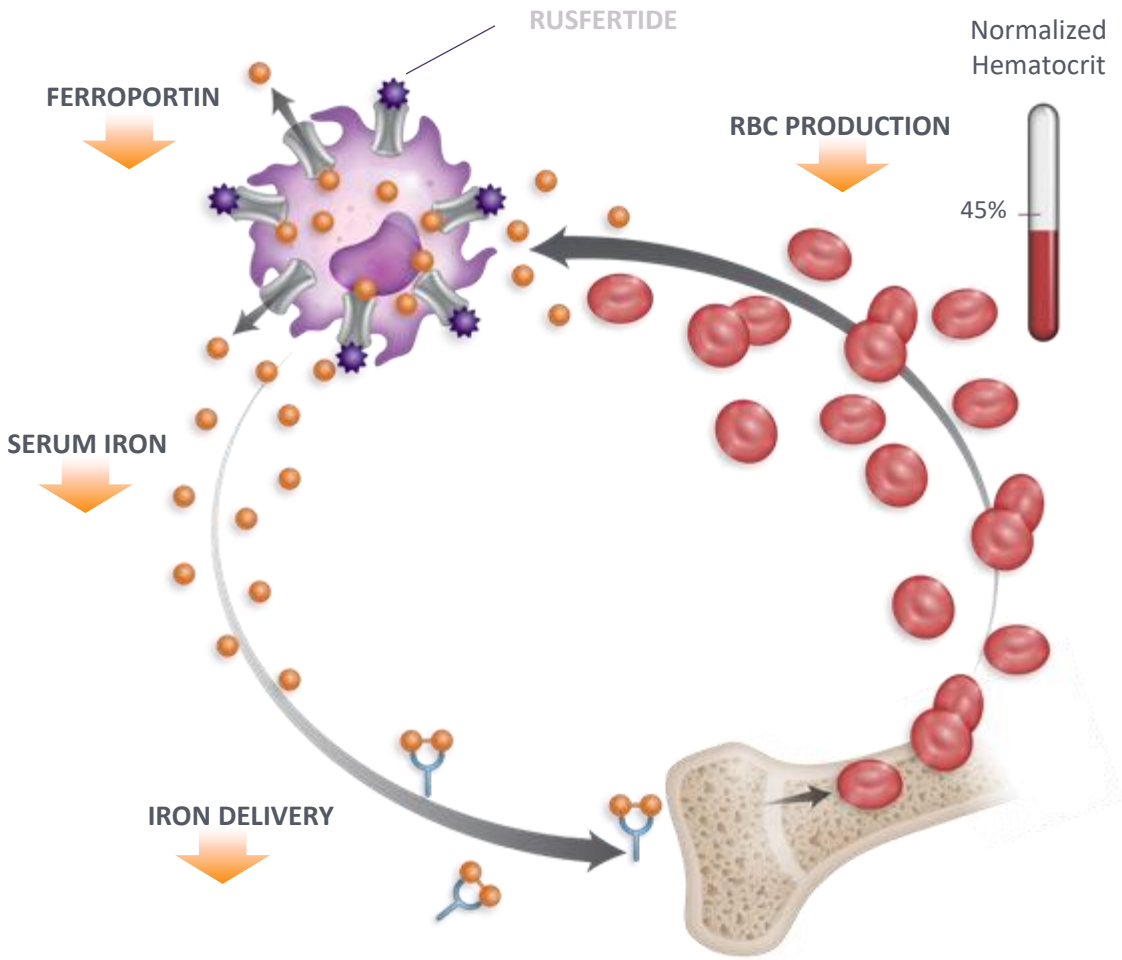
Rusfertide: Mechanistic Rationale for Potential Treatment of PV

Polycythemia Vera



MOA of rusfertide



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Rusfertide for Polycythemia Vera

Three Clinical Studies Ongoing

- Ph2 **REVIVE** Study (n=70):
  - Clinical updates presented at ASH 2021, ASCO 2022, EHA 2022, ASH 2022
    - Most recent Phase 2 data, presented at ASCO 2022, demonstrates the effects of dosing interruption and resumption
  - Randomized withdrawal study completed

- Ph2 **PACIFIC** Study (n=20):
  - High hematocrit (HCT >48%) 16-week study completed; 52-week open-label study completed in Q2 2023

- Ph3 **VERIFY** Study (n=250):
  - Study execution continues with enrollment completion expected in 1Q 2024
  - Agreed upon Phase 3 VERIFY protocol with the FDA and CHMP (EU)

- Rusfertide has **Orphan Drug** designation and **Fast Track** status

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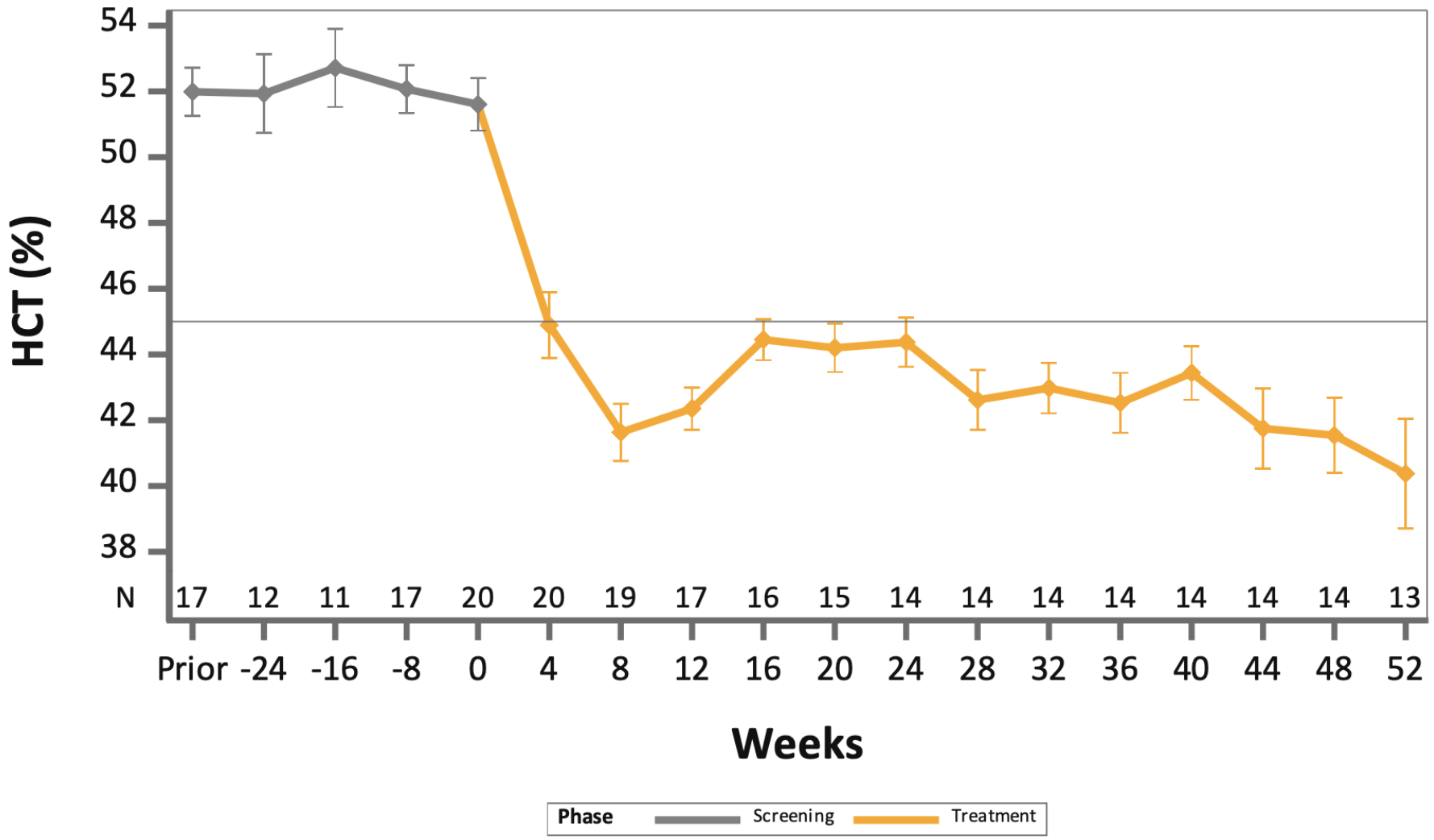
PACIFIC Study in PV Patients with High HCT (>48%)

HCT (n=17)



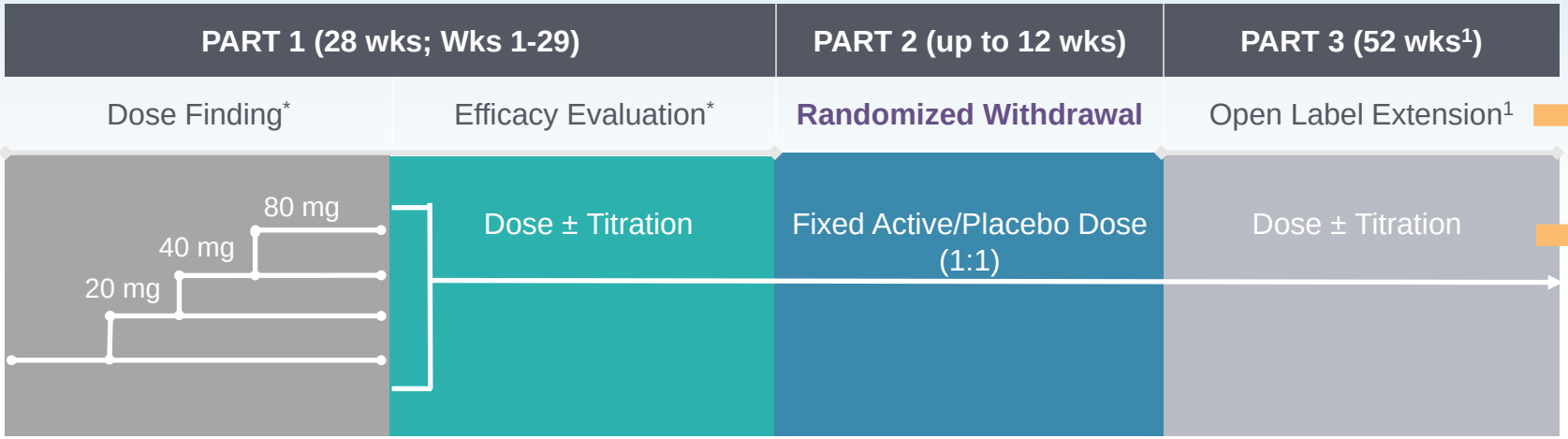
Data cutoff: April 17, 2023,
*Subjects with complete restart data

Download Date: Final

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

GOAL: Maintain Hematocrit <45%

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



[1]*OLE increased from 52 weeks to 3 years*

- *6 pts ≥ 2.5 yrs*
- *16 pts ≥ 2 yrs*
- *43 pts ≥ 1.5 yrs*
- *56 pts ≥ 1 yr*

- **Titrate every 4 weeks to maintain hematocrit < 45%*

STUDY HIGHLIGHTS:

- Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria
- ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
- Rusfertide (PTG-300) administered subcutaneously, added to prior standard therapy

KEY ENDPOINTS:

- Safety
- Maintain Hematocrit <45%
- Responder analysis
- Reduction in Phlebotomies
- Symptom Scores: MPN-SAF TSS

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[1] As of May 11, 2023

Baseline Characteristics of Study Participants in REVIVE Study

Characteristics (n = 70)

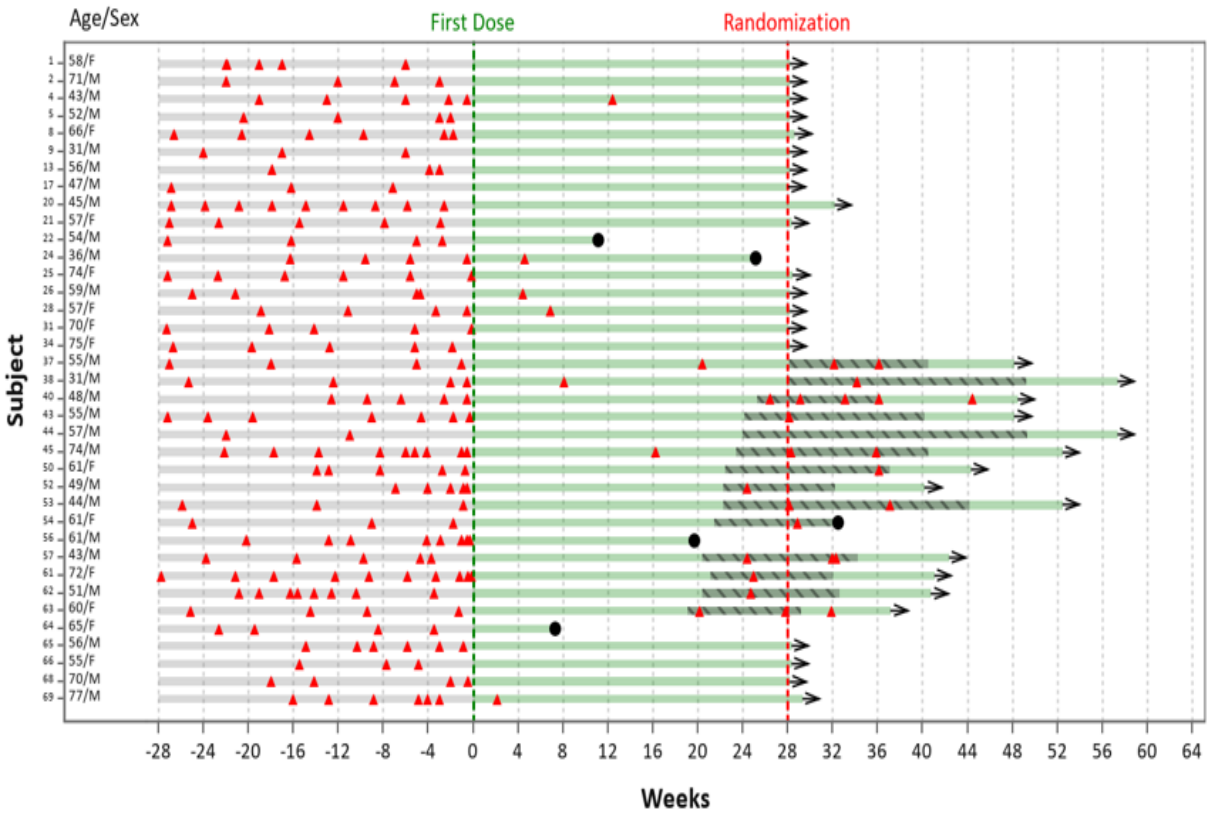
AGE	
Range	27-77 years (Mean = 57.3 yrs)
GENDER	
Females	21 (30.0%)
Males	49 (70.0%)
RISK	
Low	29 (41.4%)
High	41 (58.6%) [Age based – 37.1%, Thrombotic events – 21.4%]
DURATION SINCE PV DIAGNOSIS	
<1 yr	14 (20.0%)
1 - <3 yrs	24 (34.3%)
3 - <5 yrs	11 (15.7%)
≥5 yrs	21 (30.0%)

THERAPIES	
PHL only	34 (48.6%)
PHL + HU	21 (30.0%)
PHL + IFN	8 (11.4%)
PHL + RUX	3 (4.3%)
PHL +Multiple Agents	4 (5.7%)
NUMBER OF PHL IN 28 WEEKS PRIOR	
2-3	14 (20.0%)
4-5	38 (54.3%)
≥6	18 (25.7%)
Median	4.79
DAYS BETWEEN PHLEBOTOMIES	
Median	34

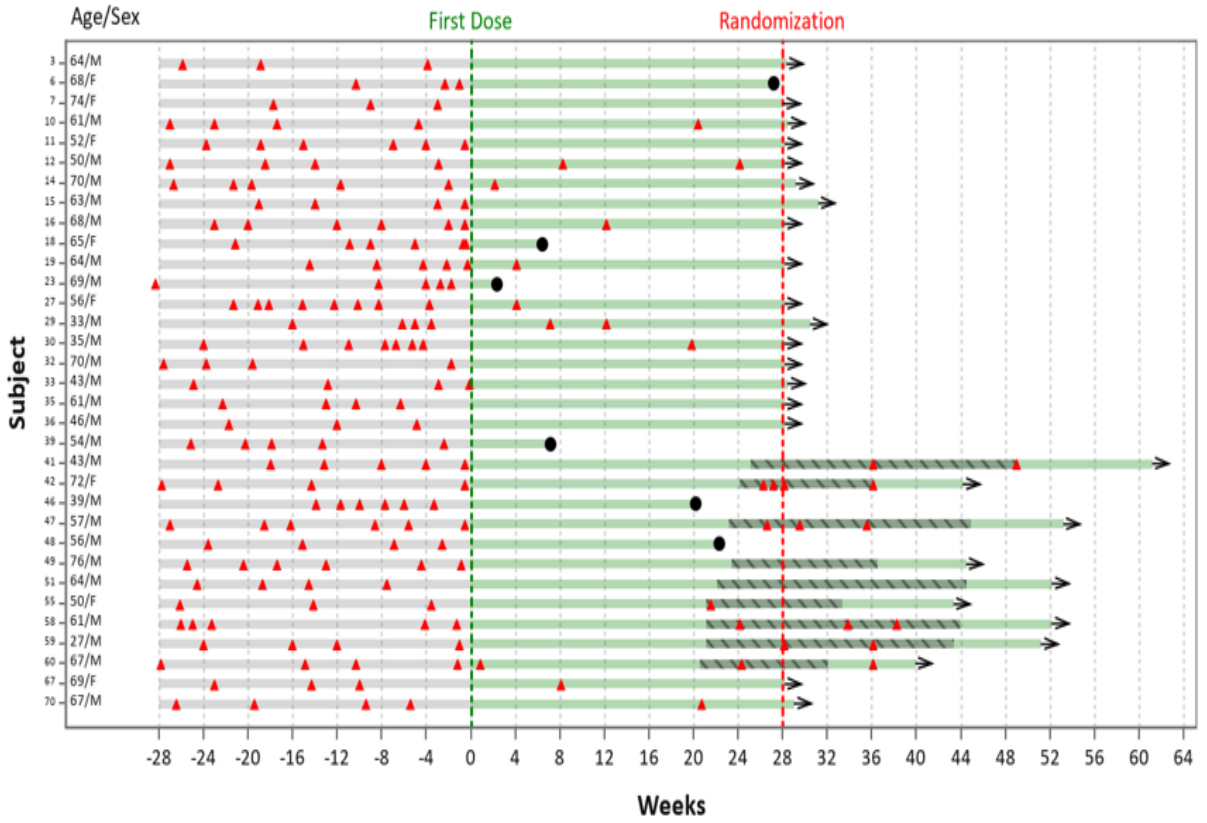
Enrollment complete. Data as of March 10, 2022, and as presented at ASCO June 2022

Meaningful Reduction in Phlebotomy Frequency During Dose Finding (Part 1)

Phlebotomy Only (n=37)



Phlebotomy + Cytoreductive (n= 33)



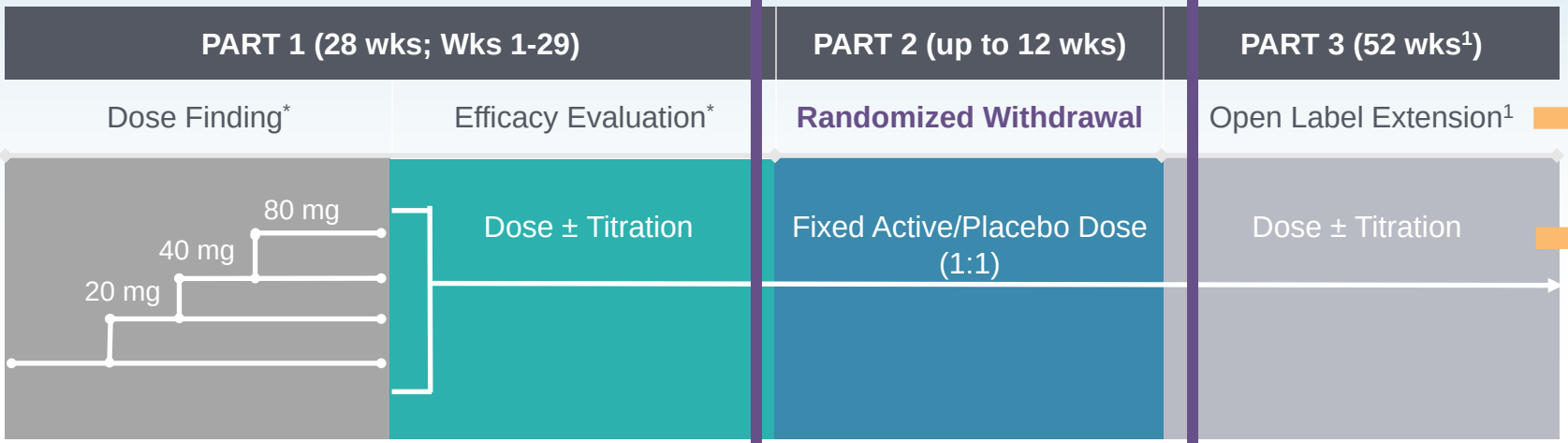
Screening | Part 1 - Dose Finding | Drug Suspension | Phlebotomy | Last Dose on Study

Data cutoff: Feb 15, 2023

Unblinding of the Randomized Withdrawal, Part 2 of the REVIVE Study

Highly Statistically Significant Results

Clinical Proof-of-Concept Study with Add-On



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- Reduction in Phlebotomies
- Symptom Scores: MPN-SAF TSS

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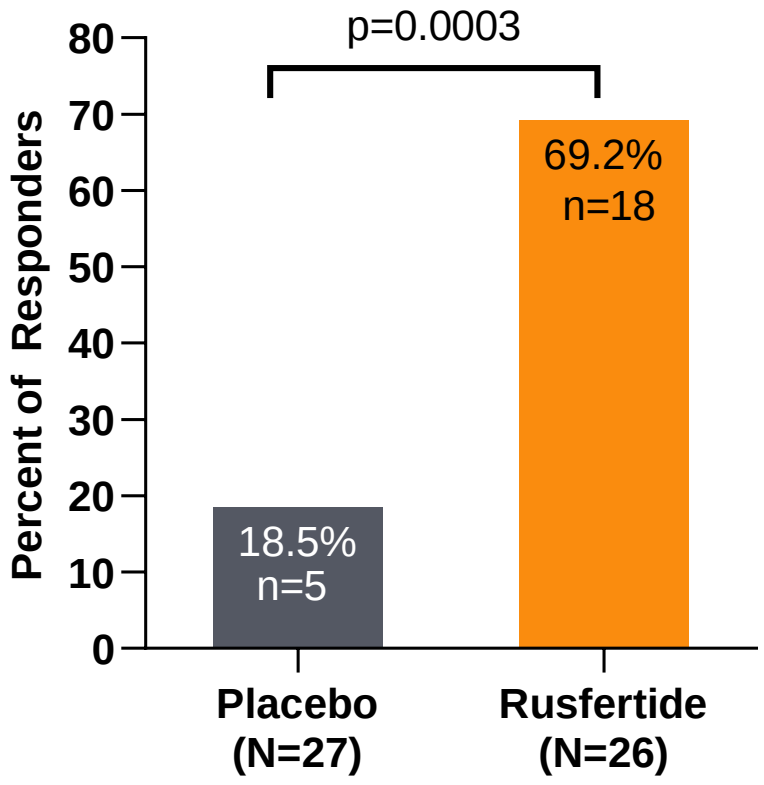
[1] As of May 11, 2023

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

Rusfertide Met the Primary Endpoint of Efficacy (p=0.0003)

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 the Part 3 open label extension part 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, the 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*

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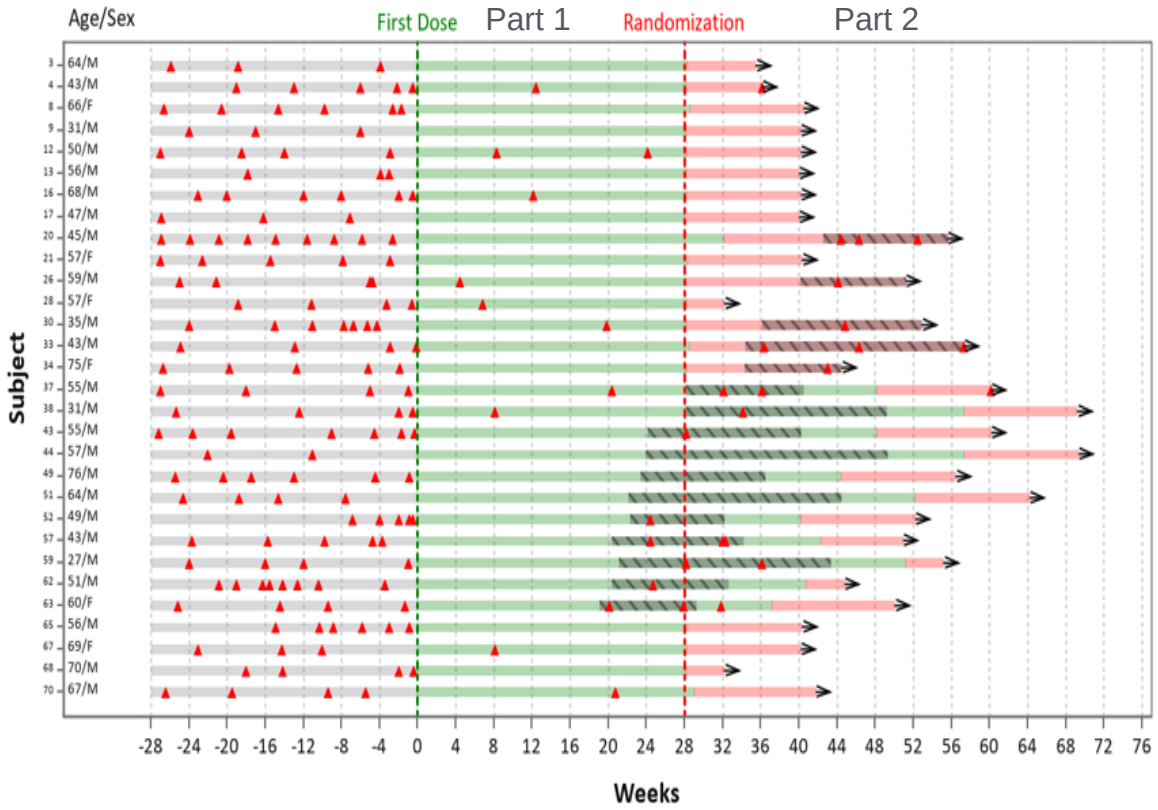
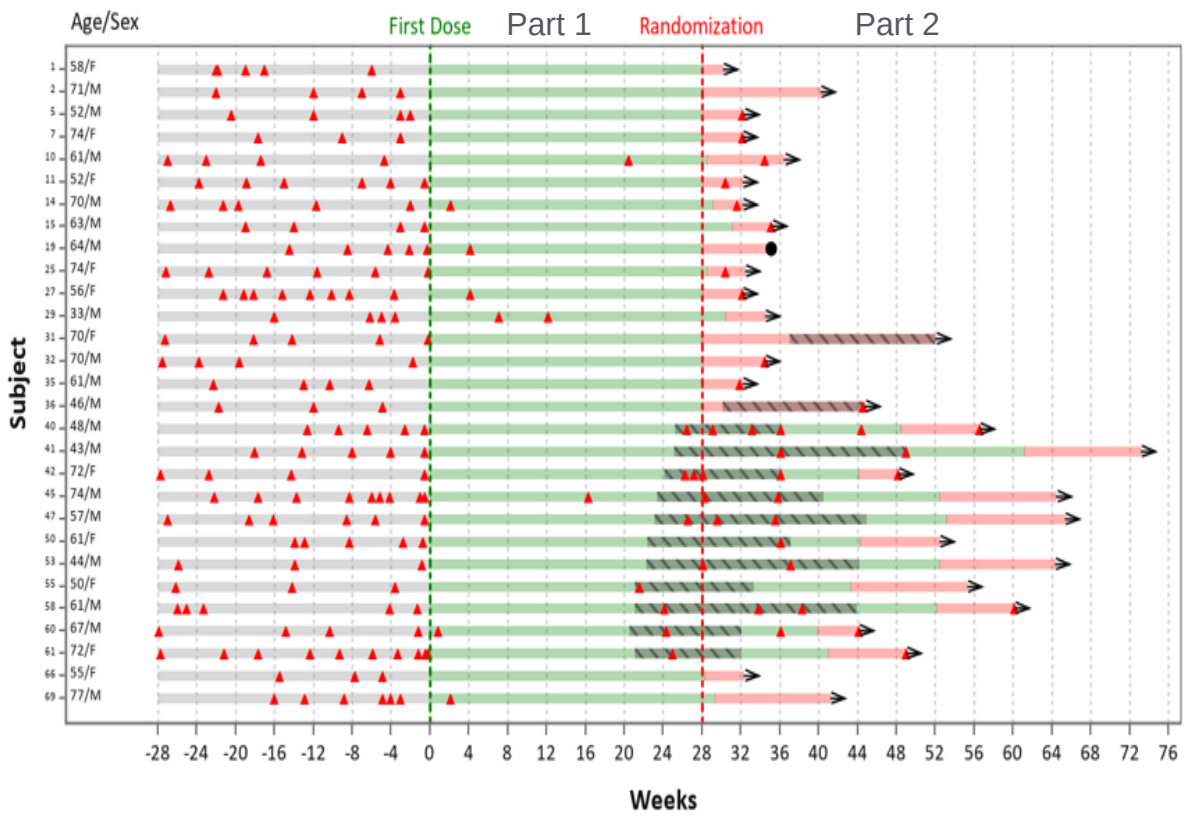
Significant Impact of Rusfertide Withdrawal During Blinded Phase (Part 2)

Rusfertide



Placebo



Screening
Part 1 - Dose Finding
Part 2 - Blinded Withdrawal
Drug Suspension
Phlebotomy
Last Dose on Study

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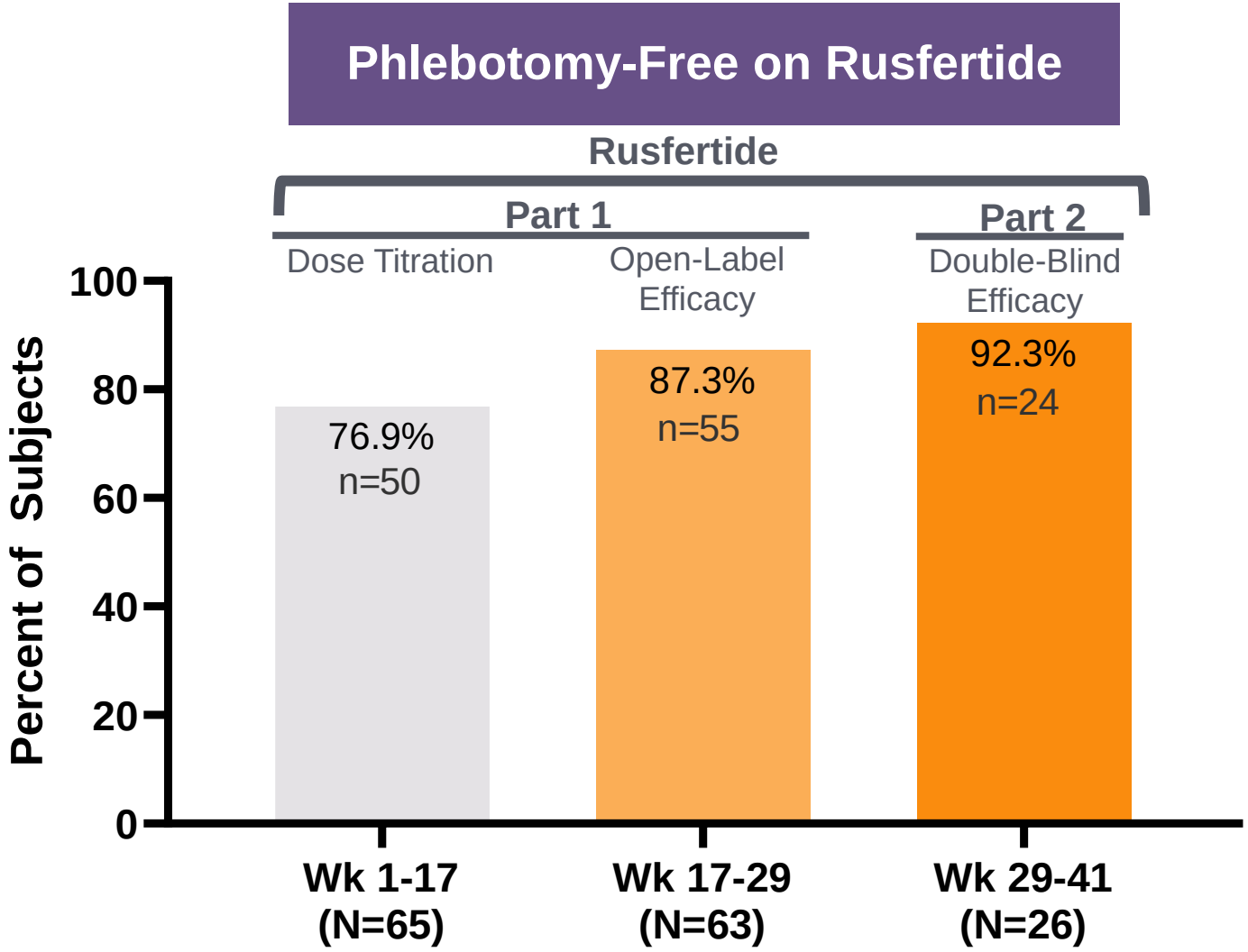
Data cutoff: Feb 15, 2023

REVIVE Study: Efficacy

Consistent Effects on Being Phlebotomy Free in Open-Label (87%) vs. Double-blind (92%) Parts of Study



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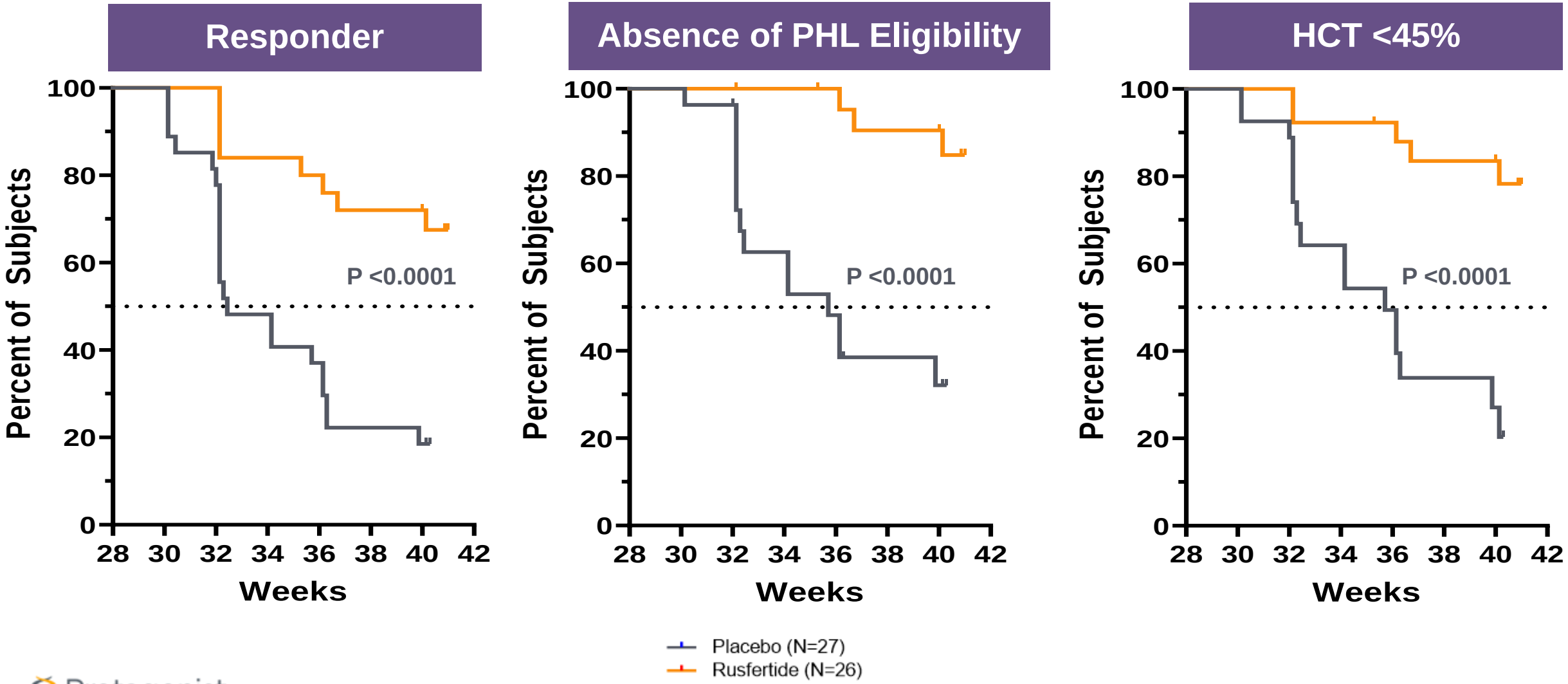
REVIVE Study: Consistent Efficacy

Rusfertide Significantly Delays Time to Event on Multiple Outcomes Compared to Placebo



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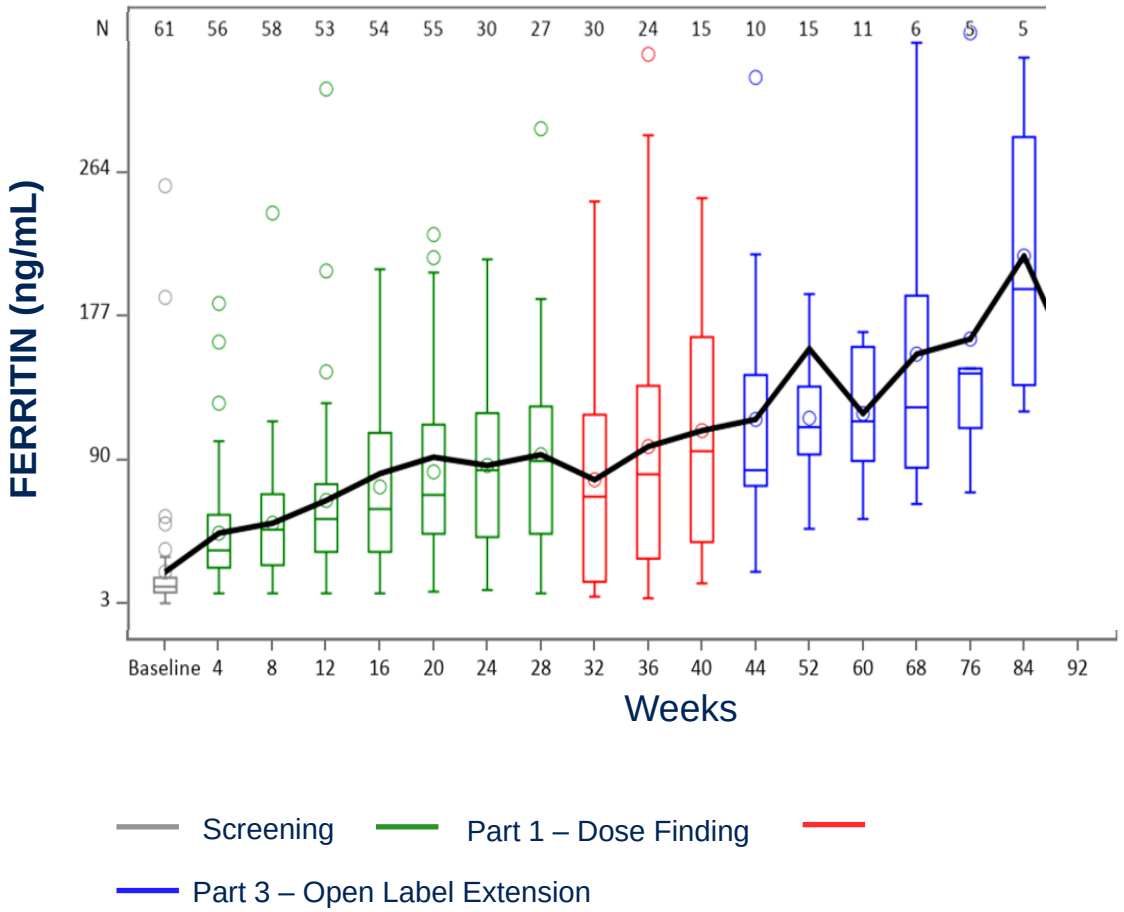
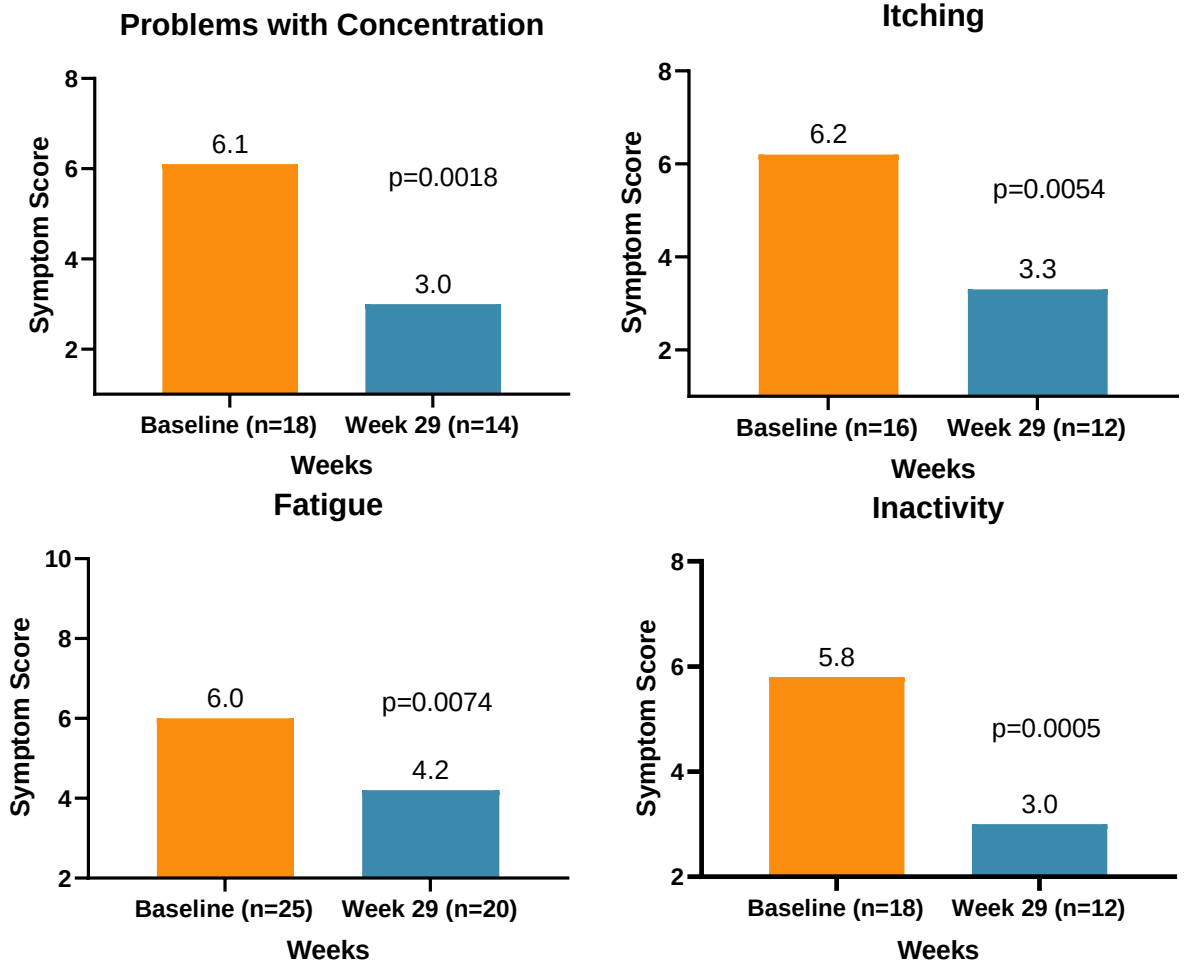
REVIVE Study: Ferritin Levels & Improvement in PV Symptoms in Part 1

Improvement in Ferritin and Symptoms - Moderate or Severe Symptoms at Baseline



Symptom Improvement in Part 1 (28-Weeks)



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

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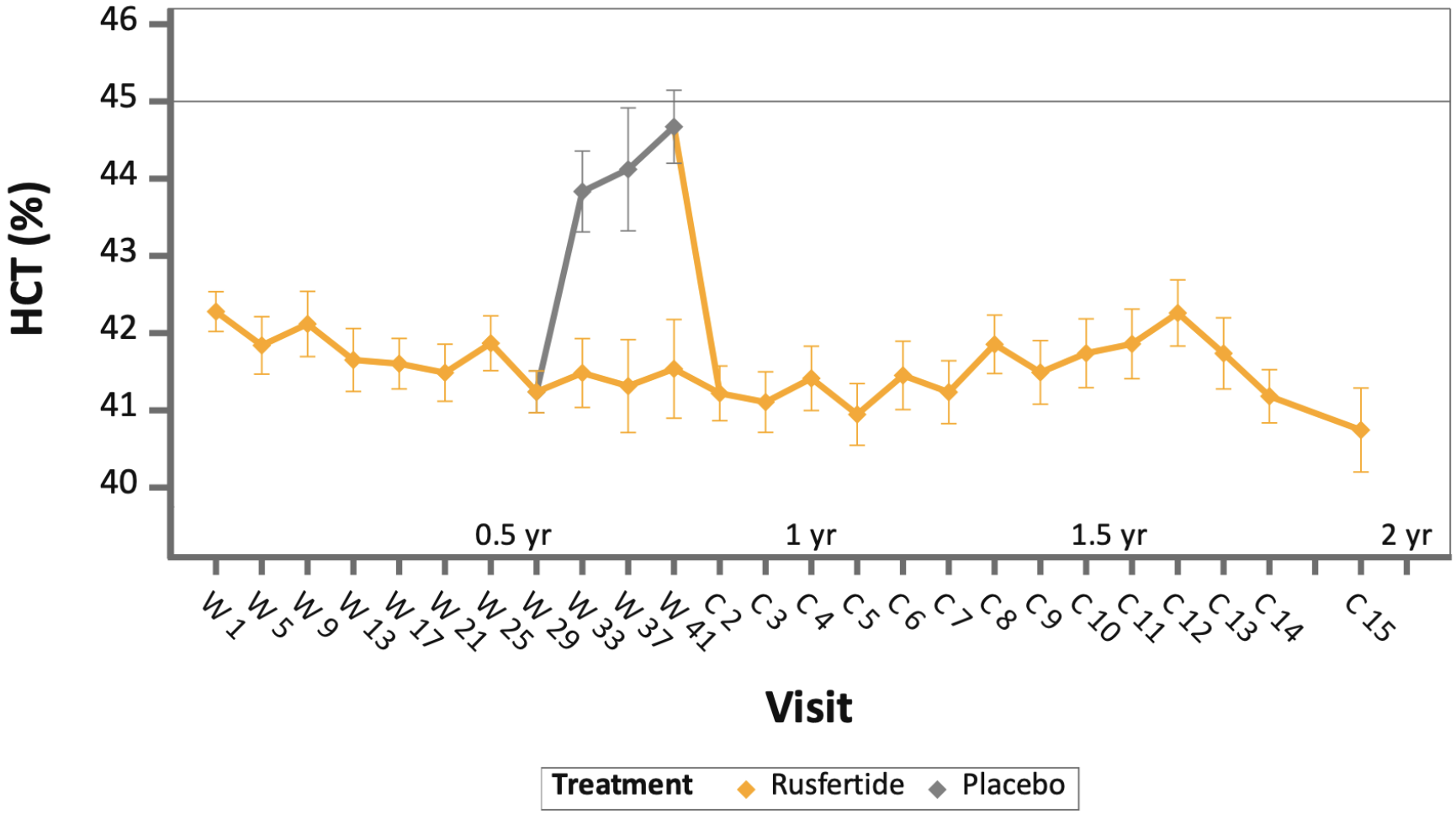
Durability of Hematocrit Control with Rusfertide in REVIVE Study



Visit: W=Week, C=Cycle, W41=C1

Download Date: 2023-05-11

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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)

Data as of 15 February 2023

- 70 subjects were enrolled in the rusfertide REVIVE study
  - 52 subjects (74.3%) have exposure ≥ 1 yr
  - 32 subjects (45.7%) have exposure ≥ 1.5 yrs
  - 10 subjects (14.3%) have exposure ≥ 2 yrs
  - 3 subjects (4.3%) have exposure ≥ 2.5 yrs
- Rusfertide was generally well tolerated
  - A majority of TEAEs were Grade 1 or 2
    - 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)

Protagonist Therapeutics

REVIVE Study: Overall Safety

No New Safety Signals

			N=70
Subjects with at least one Serious Adverse Event			13 (18.6)
Cardiac	2 (2.9)	Myocardial Infarction	1 (1.4)
		Atrial fibrillation	1 (1.4)
Gastrointestinal	2 (2.9)	Constipation	1 (1.4)
		Anogenital Dysplasia	1 (1.4)
General	1 (1.4)	Non-cardiac chest pain	1 (1.4)
Infections	1 (1.4)	Gastroenteritis	1 (1.4)
Neoplasms	7 (10.0)	Basal cell carcinoma	3 (4.3)
		Malignant Melanoma	2 (2.9)
		AML	1 (1.4)
		Squamous cell carcinoma	1 (1.4)
Nervous	3 (4.3)	Cerebrovascular accident	1 (1.4)
		Syncope	1 (1.4)
		Transient Ischemic Attack	1 (1.4)
Vascular	2 (2.9)	Peripheral artery aneurysm	1 (1.4)
		Peripheral vascular disorder	1 (1.4)

- 18.6% subjects reported an SAE
- A total of 7 subjects diagnosed with malignancy after starting the study
  - All 7 subjects had risk factors before exposure to rusfertide including pre-malignant lesions, history of cancer, or prior cytotoxic and/or cytoreductives
  - 5 out of 7 subjects had a prior malignancy
  - Most common event during the study was in situ or stage I non-melanoma skin cancer (NMSC)
  - Out of 7 subjects, only 2 have been identified since restarting rusfertide dosing in Dec 2021, after implementing mandatory dermatologic exams

Data as of 15 February 2023

Protagonist Therapeutics

Rusfertide Summary

An Investigational Injectable Hepcidin Mimetic for Treatment of Polycythemia Vera

- PV patients requiring frequent phlebotomy ± cytoreductives have been treated with rusfertide for *>2 years* in the **REVIVE** study, with subjects remaining essentially phlebotomy free
  - Rapid, sustained and durable hematocrit control
  - Robust efficacy in all categories of patients
  - Rusfertide dosing was interrupted and led to loss of effect; restart restored therapeutic benefits
  - Positive improvements in symptom scores
  - 53 patients, 1:1 randomization part 2 of the study completed

- Rapid HCT control (<45%) without phlebotomy in high HCT (>48%) **PACIFIC** study

- Rusfertide treatment with or without cytoreductives appears to be well tolerated
  - Safety update presented at ASH, December 2022; no new safety signals observed[1]

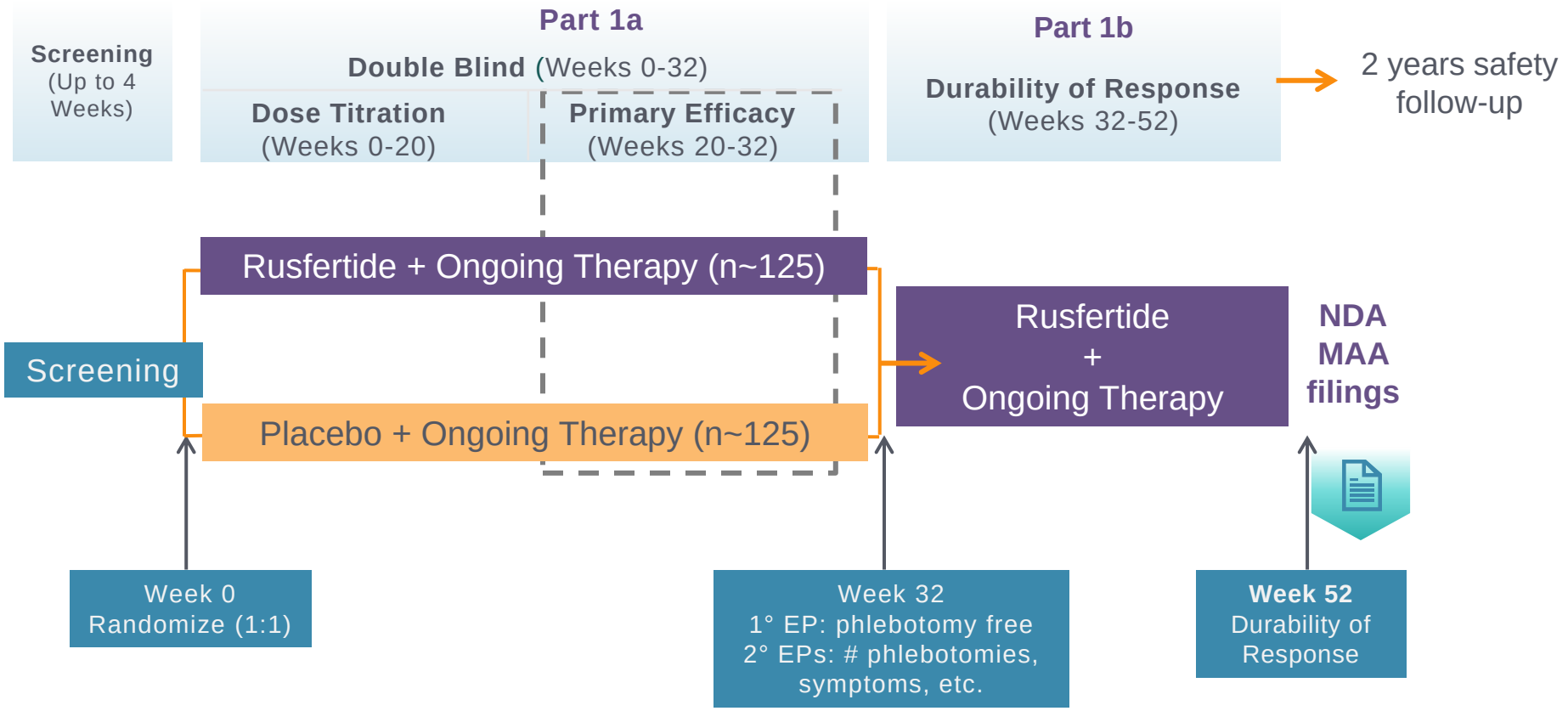
- ~250 patient, randomized, placebo-controlled Ph3 **VERIFY** study to confirm efficacy and safety
  - Execution underway, enrollment completion by 1Q 2024

Protagonist Therapeutics

1. Pemmaraju, Naveen, et al. "Subgroup Analysis of Adverse Events Following Rusfertide Dosing in Revive: A Phase 2 Study of Patients with Polycythemia Vera." *Blood* 140.Supplement 1 (2022): 6835-6837.

Randomized, Double-blind, Placebo-Controlled Phase 3 **VERIFY** PV Study

Ongoing Study of N~250 Subjects

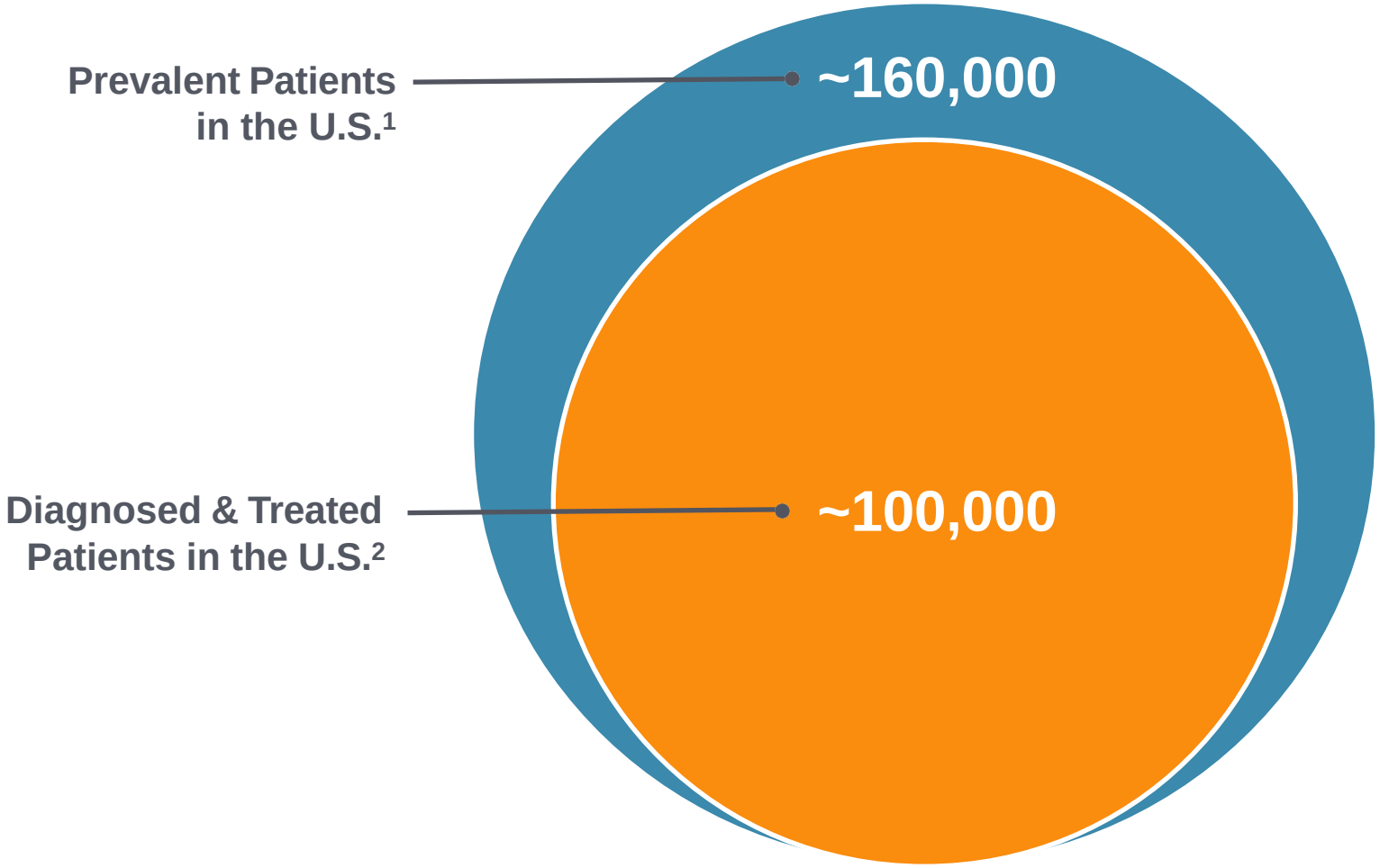


Ph3 study design capitalizes on the successful outcome to date of the Ph2 REVIVE Study

In consultation with the U.S. Food and Drug Administration, Protagonist has implemented a set of safety monitoring procedures in all ongoing clinical studies, including cancer surveillance measures (dermatological examinations) and stopping rules.

Protagonist Therapeutics

PV Market Overview



Rusfertide has the potential to create a new standard of care in PV

- ✓ Broad spectrum of patients
- ✓ Competition with distinct limitations
- ✓ High unmet needs with uncontrolled patients

1. Based on NORD estimates (44 to 57 per 100,000 people in the US) **2.** Internal estimates based on data on file

Identifying PV Patients with Moderate Treatment Burden

Defining the "moderate burden" population using current market treatments and trends is the key to understanding rusfertide's market opportunity

Representative events to identify uncontrolled period for a PV patient

Outcome of an uncontrolled phase

Phlebotomy Frequency

An increase in frequency of phlebotomies indicates the intervention is not working to maintain HCT

Dosing Fluctuations

Dosage fluctuations can signify that there is a need for an altered treatment paradigm. High doses of HU (1-2 g/day) can also indicate difficult-to-control PV

Treatment Switches

Switching treatments (between products or interventions) posits that physicians are looking for a more efficacious treatment

Symptoms

Patients with symptoms like fatigue and cognitive dysfunction have persistent unmet needs despite current treatment

Thrombotic Events

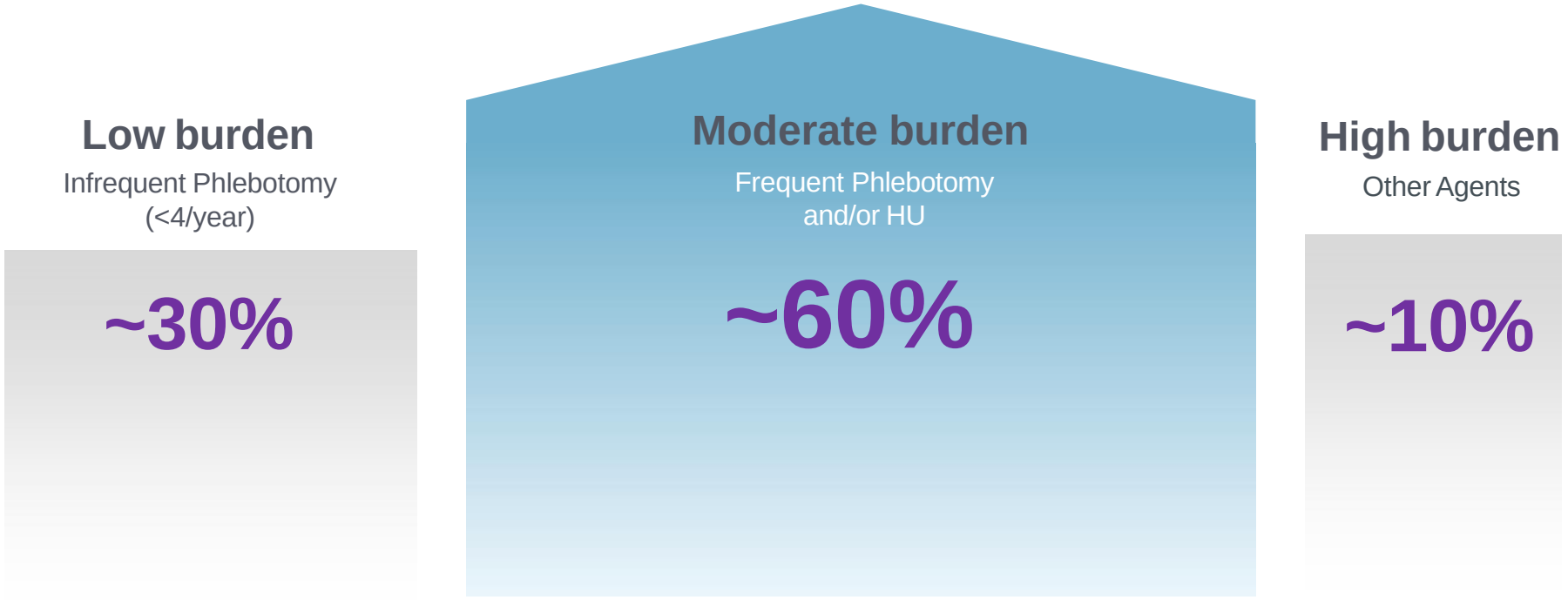
Occurrence of thrombotic events post treatment initiation is an indicator of the ineffectiveness of the treatment - one of the definitive examples of an "uncontrolled" PV patient

Protagonist Therapeutics

Potential Commercial Positioning for Rusfertide

Therapy of Choice for Patients Experiencing Moderate Treatment Burden to Achieve HCT Control

Rusfertide Target



Most patients receiving phlebotomy and/or HU have inconsistent and uncontrolled HCT. Rusfertide, a hepcidin mimetic, can potentially benefit a broad spectrum of patients by enabling consistent and continuous control of HCT <45%.

Protagonist Therapeutics

Illustrative rusfertide target. Percentages derived from 100,000 diagnosed and treated patients in the US
Estimates based on Protagonist internal research, data on file

Protagonist Therapeutics

JNJ-2113 (formerly PN-235): IL-23 Receptor Antagonist

Oral Targeted Investigational Therapy for Psoriasis and Other IL-23 Mediated Diseases

Protagonist-Janssen Oral, IL-23R Antagonist Collaboration

Collaboration overview

- Initiated in 2017 with I&I market leader Janssen Biotech[1]
- JNJ-2113 (formerly PN-235) jointly discovered using Protagonist's proprietary peptide discovery platform
  - Protagonist completed pre-clinical and Phase 1 studies
  - Janssen responsible for further development and commercialization

Collaboration economics

- Protagonist eligible for up to $855M in development and sales milestones and upward-tiering royalties for JNJ-2113 and other collaboration compounds

Recent clinical data; development status

- Phase 2B FRONTIER 1 data presented at WCD 2023 (July 2023)
- Phase 3 psoriasis study planned
- Phase 2b UC study planned (Q4 2023)

JNJ-2113 potential best-in-class oral agent

- Potential to expand IL-23 market to oral therapy

Protagonist Therapeutics

[1]Stelara® generated $9.7B in sales, and Tremfya® generated $2.7B in sales in 2022, per Johnson & Johnson 2022 Annual Report. Stelara® and Tremfaya® not part of Protagonist-Janssen collaboration.

IL-23R Antagonist Market Overview

Multi-billion Market Opportunity for an Oral Agent

Significant market potential for IL-23R antagonist

- Relevant indications include psoriasis, psoriatic arthritis, IBD (ulcerative colitis, Crohn's disease)
- Psoriasis prevalence = 125M WW patients[1] (8M US[1])
  - 30% develop psoriatic arthritis
- $13.2B major market sales for psoriasis (2020)[2]
  - Projected growth to $25.3B in 2030[2]
- $14.2B major market sales for IBD (2020)[2]
  - Projected growth to $24.9B in 2029[2]

Oral agents expected to contribute to market growth

- Substantial portion of patients untreated with current standard of care
  - 25% of treated psoriasis patients treated with biologics[1]
- Despite strong efficacy, biologics associated with safety concerns, loss of response, inconvenient administration, highlighting the need for safe and effective oral options[3, 4]

Protagonist Therapeutics

1. Evaluate Pharma 2022; 2. GlobalData 2020; 3. Levin, E. et al. *J Dermatol Treat*; 25(1); 78-82; 4. Piragine E., et al. *J Clin Med 2022*; 11(6); 1506

Psoriasis Treatment Overview

JNJ-2113 is a Potential First, Best, Only-in-Class Drug Candidate

JNJ-2113 (formerly PN-235) Oral IL-23 Receptor Antagonist	**Injectable IL-23 antagonists** demonstrate robust efficacy and safety in psoriasis

• Biological target: IL-23 receptor
• Drug delivery: Oral
• Chemical modality: Peptide
	• Potential for oral IL-23 pathway inhibitors to substantially expand market beyond injectable biologics
	• Pan-JAK and selective JAK1/3 inhibitors have black box warnings' Approved in IBD but not approved in psoriasis due to risk-benefit
	• The TYK2 inhibitor Sotyktu was recently approved in psoriasis
	  • Most effective oral medicine but not as effective as the IL-23 and IL-17 antagonists
	  • No black box warnings like other JAK inhibitors but limited long-term safety experience
	  • TYK2 inhibitors are small molecule approaches with a low barrier to entry and multiple competitors
	  • BMS/Sotyktu, Takeda/TAK279

Protagonist Therapeutics

JNJ-2113 (PN-235)

Multiple Clinical Studies in Progress and Planned

- **Planned**
  - Phase 3 study for moderate-to-severe plaque psoriasis
  - Phase 2b study for ulcerative colitis
- **FRONTIER 1**
  - 255 patient Phase 2b placebo-controlled study in moderate-to-severe plaque psoriasis
  - Oral tablet dosing, qd and bid
  - Topline data summary; March 07, 2023
- **FRONTIER 2**
  - Long term extension study; ongoing
- **SUMMIT**
  - 90 patient Phase 2 placebo-controlled study in moderate-to-severe plaque psoriasis
  - Oral once daily delayed release tablets
  - Completed April 10, 2023
- **Other**
  - Phase 1 study in healthy volunteers; completed (by Protagonist)
  - NCT05062200: Phase 1 study in healthy Japanese and Chinese participants; completed
  - NCT05703841: Phase 1 study in healthy Chinese adult participants; completed

JNJ-2113 Characteristics

Preclinical, Phase 1 and Phase 2b Data Supportive of a Robust Clinical Development Program

- **Highly potent (single digit picomolar) oral IL-23R antagonist:**
  - >1000-fold more potent vs first-generation candidate (PBMC, phospho-STAT3 assay)
  - Similar or better target affinity vs. IL-23 mAbs
- **High oral stability:**

  Ex-vivo stability: >24hr half-life in feces (human, cyno, and rat)

  In-vivo stability: >25% fecal recovery after 24hrs in cynos

- **Pre-clinical Proof-of-Concept:**
  - Achieved pre-clinical PoC with oral dosing in IL-23-induced rat ear skin inflammation model
  - Similar inhibition to systemic IL-23 mAbs
- **Phase 1 study in NHVs:**
  - Inhibition of IL-23 pathway related biomarkers comparable to approved IL-23 mAbs
- **Phase 2b FRONTIER1 study in Psoriasis:**
  - Potential for best-in-class oral agent for psoriasis

Protagonist Therapeutics

ISID – Fourie A, et al. First-in-Class Oral Peptide Systemically Targeting the IL-23 Pathway. Abstract presented at the International Societies for Investigative Dermatology; May 2023

WCD – Bissonnette R, et al. A Phase 2, Randomized, Placebo-controlled, Dose Ranging Study of Oral JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis: FRONTIER 1. Late Breaking Abstract presented at the World Congress of Dermatology; July 2023

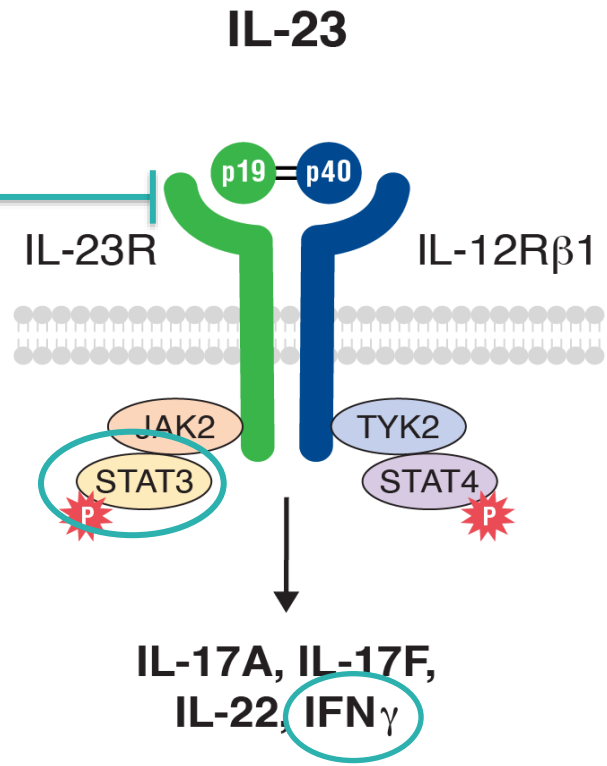
In Vitro Pharmacology

- JNJ-2113 is a competitive peptide antagonist that binds with high affinity to IL-23R, and selectively inhibits IL-23 proximal signaling and downstream cytokine production with high potency

- Binds with high affinity (K_D 2 pM) to human IL-23R (SPR)

- Potently inhibits (IC_{50} 6 pM) IL-23-induced proximal signaling (human PBMC pSTAT3)
- No inhibition of IL-12-induced pSTAT4

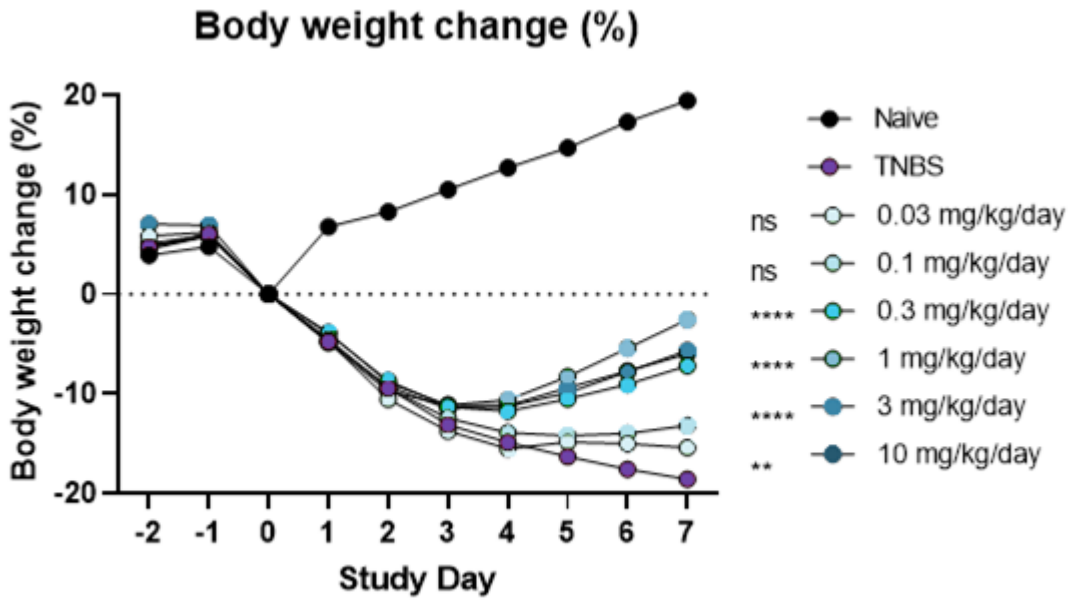
- Potently inhibits IL-23-induced IFNγ in human NK cells (IC_{50} 18 pM) and human whole blood (IC_{50} 11 pM)
- Similar IC_{50} range in blood from PsO patients

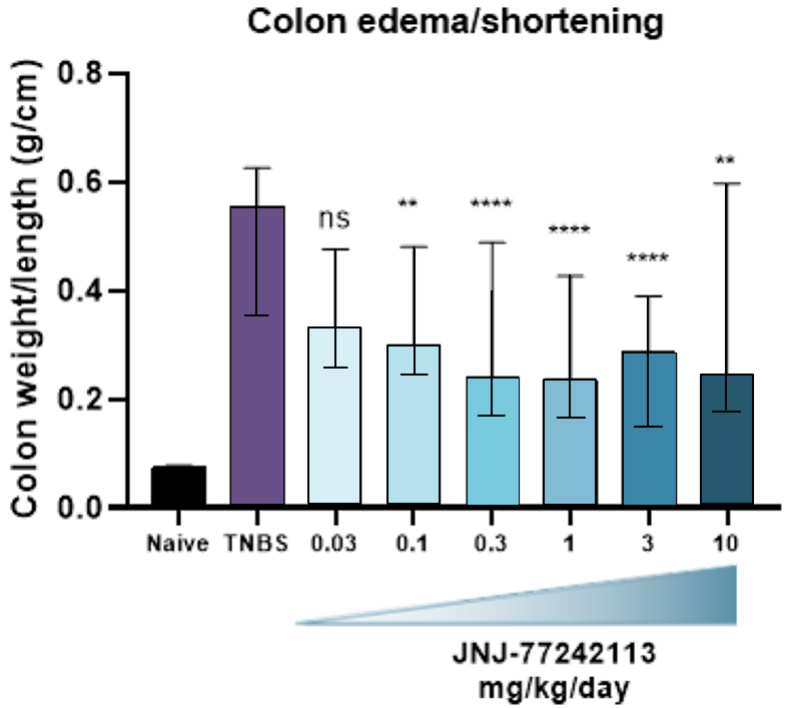


IC_{50}=50% inhibitory concentration; K_D=Dissociation constant; NK=Natural killer; PBMC=Peripheral blood mononuclear cells; SPR=Surface plasmon resonance; STAT=Signal transducer and activator of transcription.

Fourie A, et al. ISID Meeting; May 10-13, 2023; Tokyo, Japan.

Orally Dosed JNJ-2113 Attenuates Weight Loss and Colon Inflammation in the Rat TNBS-induced Colitis Model



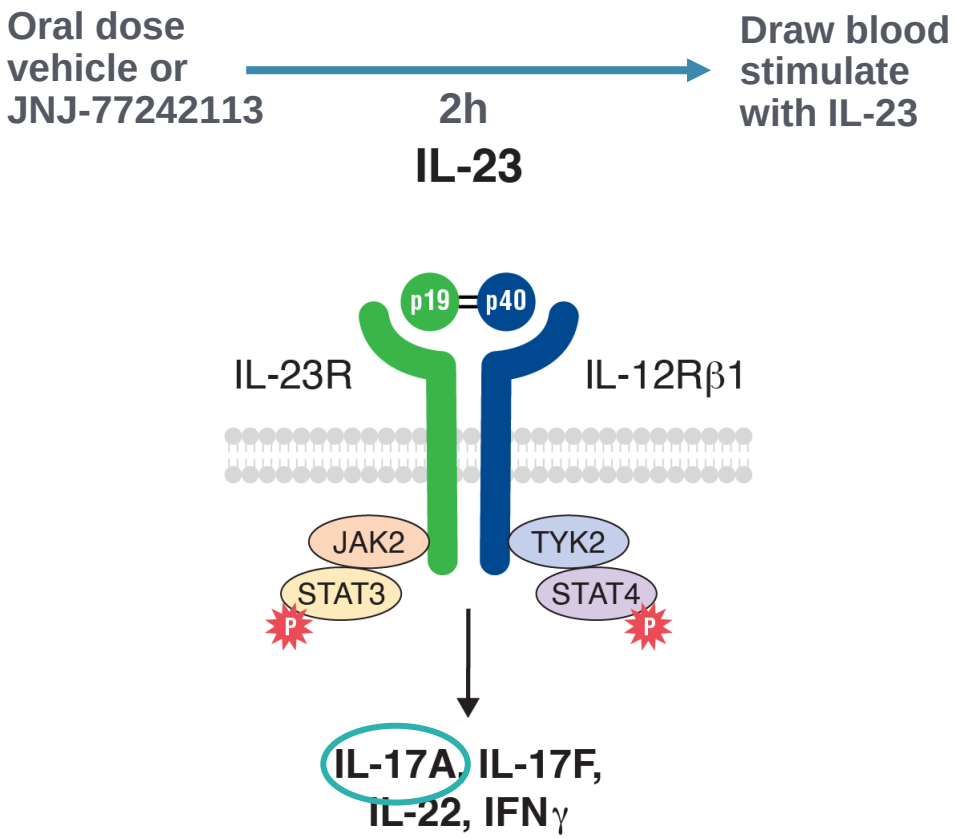


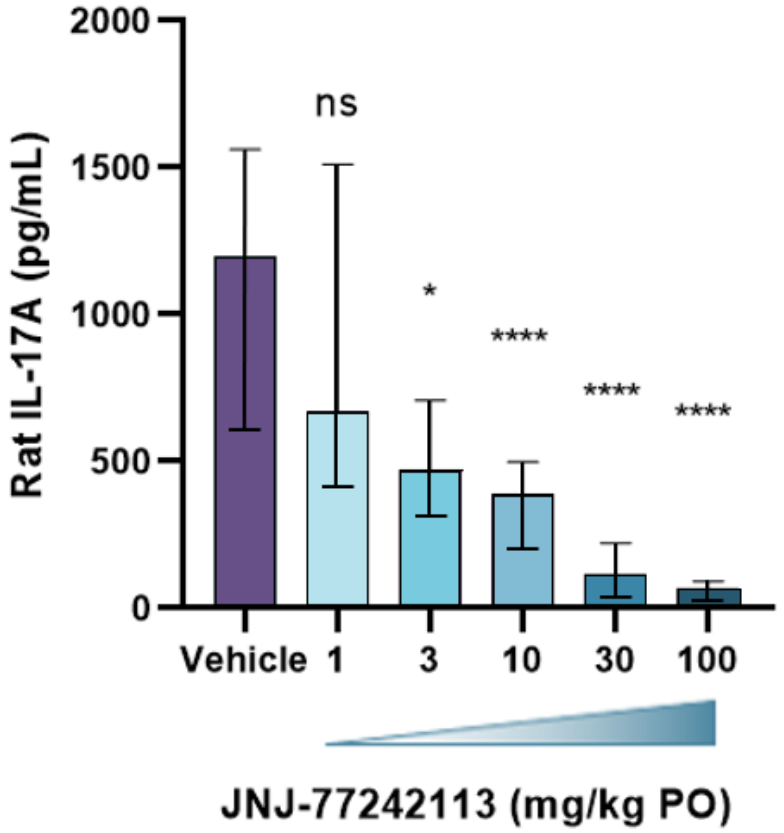
- Statistically significant effects seen beginning at doses of 0.1 to 0.3 mg/kg/day
- Although exposure in plasma and skin was much lower than GI tissues, exquisite potency of JNJ-2113 indicated potential for systemic activity beyond the GI tract

GI=Gastrointestinal; TNBS=Trinitrobenzenesulfonic acid.
ns=not significant, **p <0.01, ****p <0.0001. Graph on right represents median and interquartile range. Data combined from three studies.

Fourie A, et al. ISID Meeting; May 10-13, 2023; Tokyo, Japan.

Orally Dosed JNJ-2113 Shows Systemic Pharmacodynamic Activity in Rat Blood





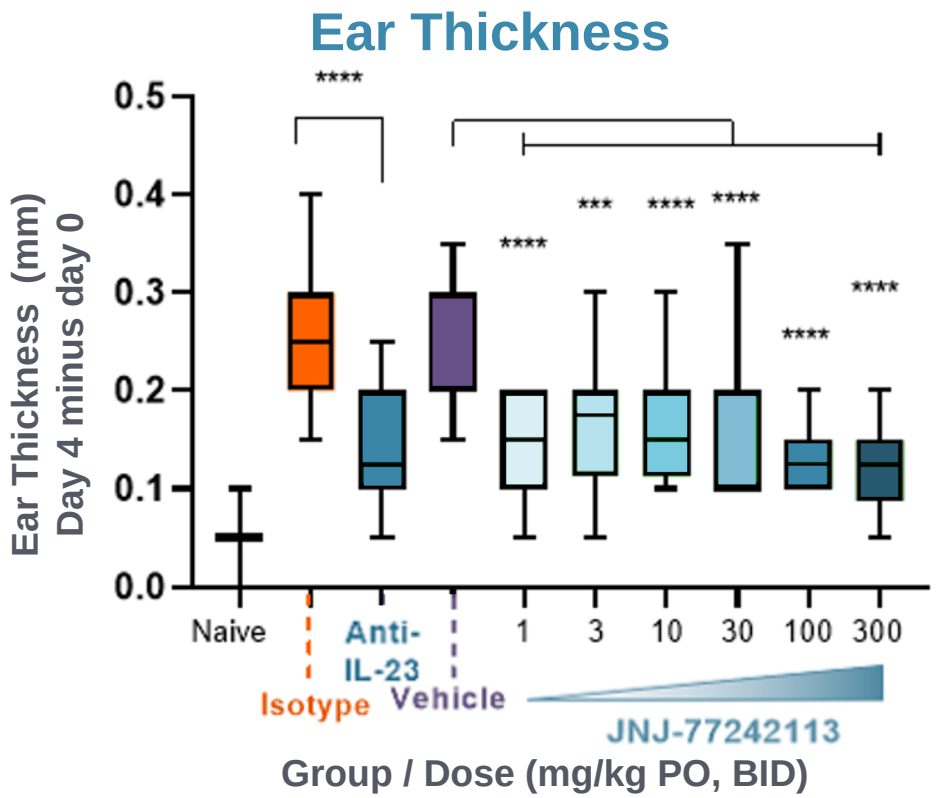
- Dose-dependent inhibition of *ex vivo* IL-23-stimulated IL-17A production in rat blood

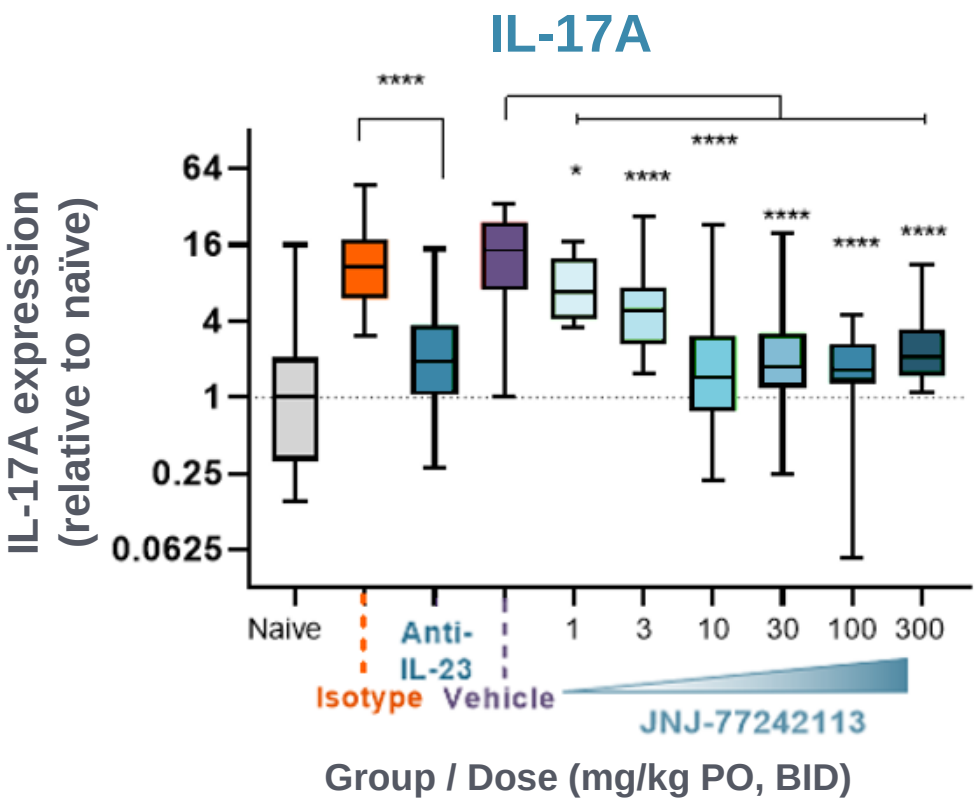
ns=not significant, *p <0.05, ****p <0.0001. Graph represents median and interquartile range. Data from five different experiments were combined.

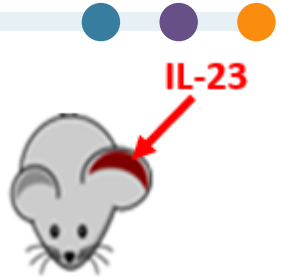
Protagonist Therapeutics

Fourie A, et al. ISID Meeting; May 10-13, 2023; Tokyo, Japan.

Oral JNJ-2113 Achieves Inhibition of IL-23-induced Rat Skin Inflammation Equivalent to Anti-IL-23 Antibody







- Doses ≥ 1 mg/kg BID reduced inflammation and cytokine induction (IL-17A, IL-17F and IL-22)
- Doses ≥ 10 mg/kg BID showed equivalent inhibition to an anti-IL-23 antibody

BID=Twice daily. Anti-IL-23 and isotype control dosed intraperitoneally on days -1 and 3.
ns=not significant, *p <0.05, ***p <0.001, ****p <0.0001. Boxes depict median and interquartile ranges; bars depict minima and maxima. Data combined from three experiments.

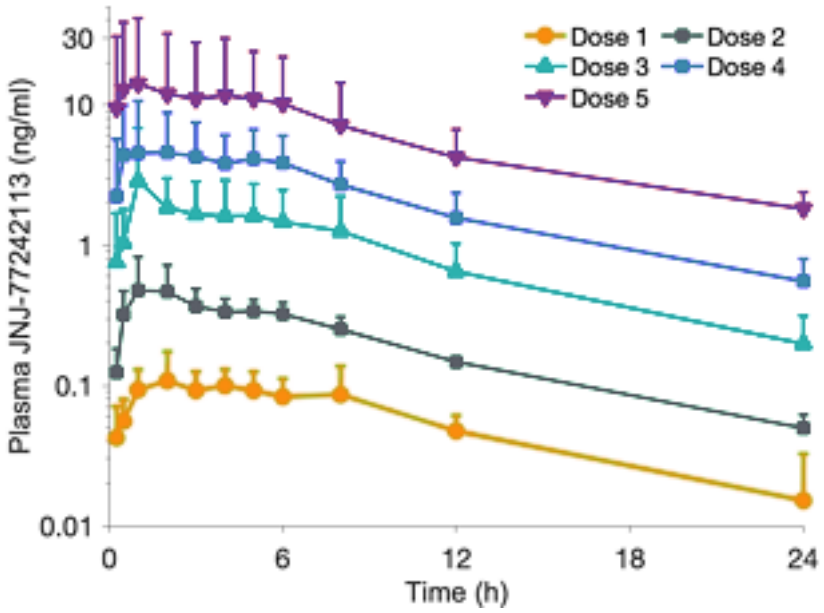
Protagonist Therapeutics

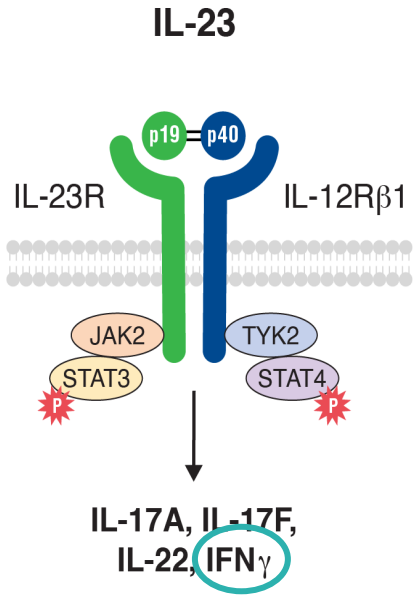
Fourie A, et al. ISID Meeting; May 10-13, 2023; Tokyo, Japan.

JNJ-2113 Phase 1 Study: Safety, Pharmacokinetics, Systemic Pharmacodynamics

- Single and multiple oral doses were safe and generally well tolerated with no safety signal of concern

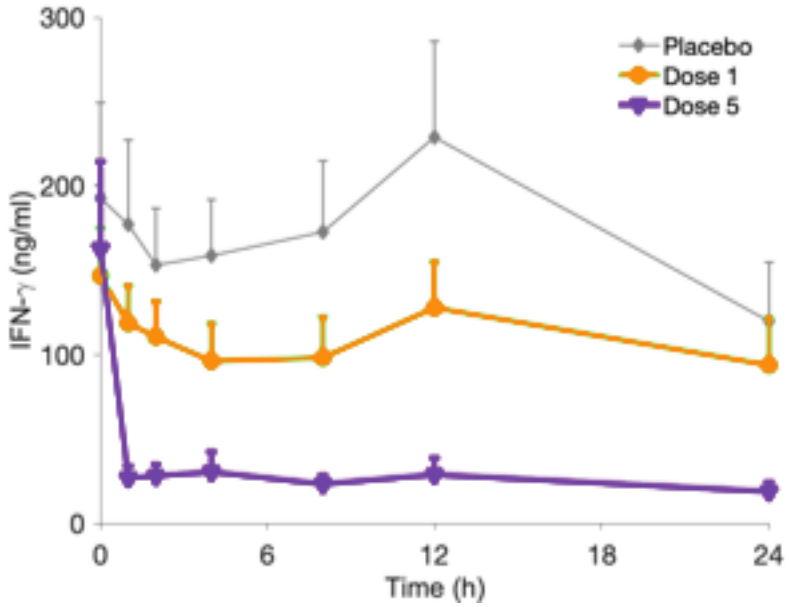
Human PK profile† supports pathway coverage





Systemic PD: *ex vivo* IL-23-induced IFNγ in blood

Robust systemic PD activity with oral dosing



- Demonstrated PoC for systemic PD activity of orally dosed JNJ-2113 in humans
- Phase 2 dose ranging study in patients with moderate-to-severe PsO completed in February 2023

PD=Pharmacodynamic; PK=Pharmacokinetic; PoC=Proof of Concept.
PK data represent mean + SD.
†Phase 1 conducted under fasted conditions.

Protagonist Therapeutics

Fourie A, et al. ISID Meeting; May 10-13, 2023; Tokyo, Japan.

JNJ-2113 FRONTIER 1 Phase 2b Plaque Psoriasis (PsO) Study

A Phase 2b multicenter, randomized, placebo controlled, dose-ranging study to evaluate the efficacy and safety of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis

Adult Patients with PP

N=255

Eligibility:

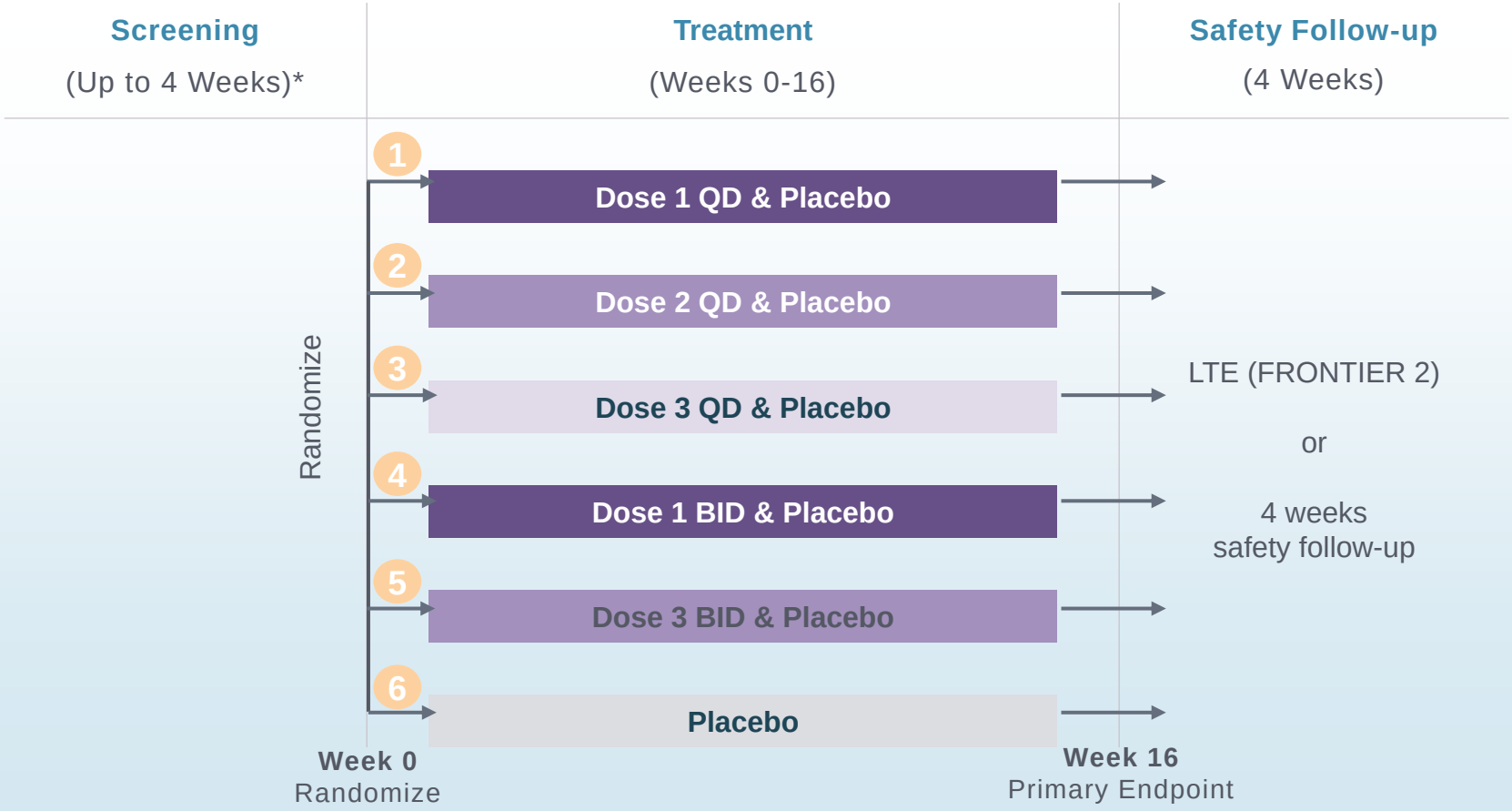
- Moderate – Severe PP

Inclusion:

- BSA ≥ 10%
- PASI ≥ 12

Primary endpoint:

- PASI ≥ 75 at Week 16



Protagonist Therapeutics

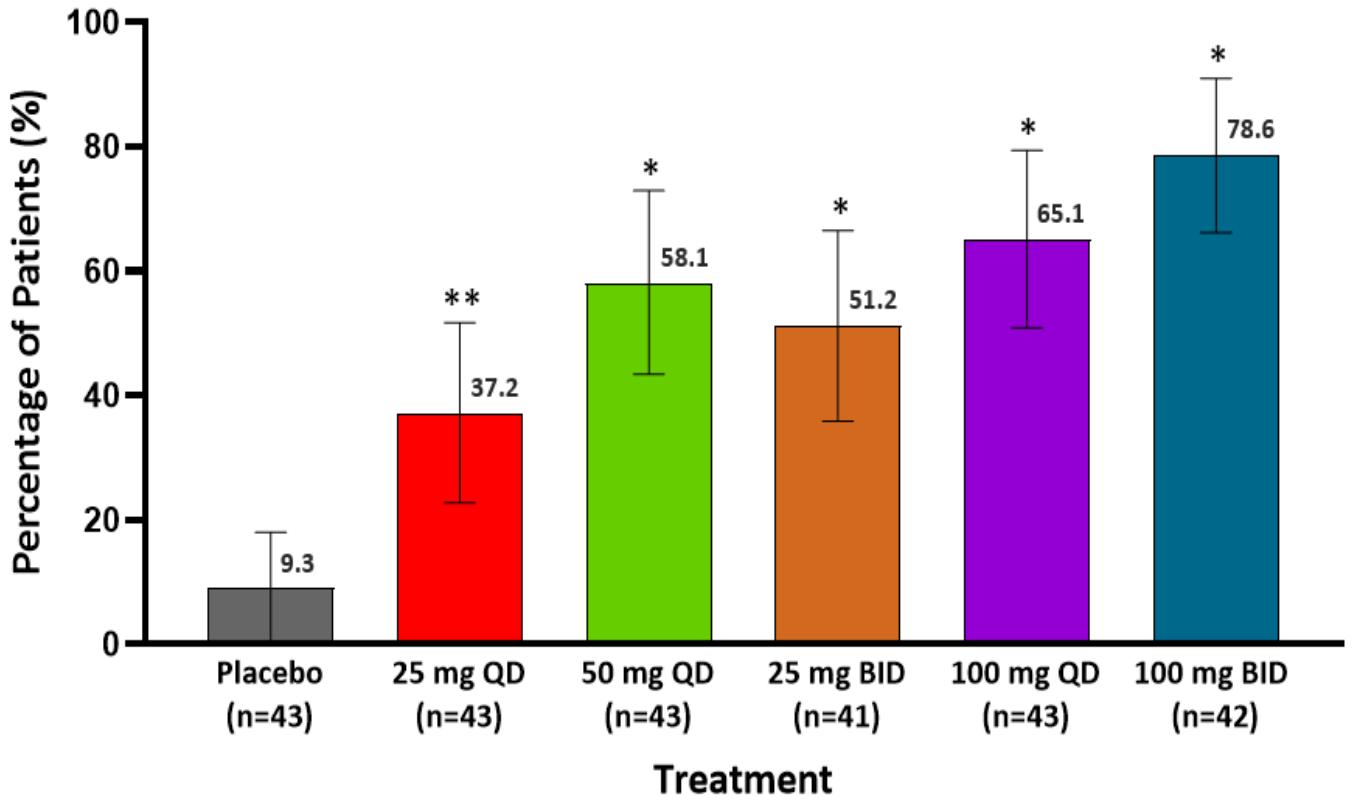
Demographics and Disease Characteristics at Baseline

	Placebo	JNJ-77242113						Total
		25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID	Combined*	
Full analysis set	43	43	43	41	43	42	212	255
Age (yrs)	43.9 (14.70)	44.5 (12.72)	45.1 (11.08)	45.7 (11.91)	44.7 (14.11)	42.0 (11.34)	44.4 (12.24)	44.3 (12.65)
Weight (kg)	92.1 (24.66)	89.0 (19.42)	87.6 (19.23)	90.8 (22.12)	85.4 (22.49)	88.5 (16.94)	88.2 (20.03)	88.9 (20.87)
BMI (kg/m²)	31.2 (7.61)	30.0 (7.25)	29.3 (5.97)	30.2 (6.72)	28.8 (7.39)	30.0 (5.40)	29.6 (6.55)	29.9 (6.75)
PsO disease duration (yrs)	17.9 (14.37)	15.5 (11.76)	21.5 (11.16)	18.1 (11.82)	19.5 (13.34)	16.7 (13.78)	18.3 (12.48)	18.2 (12.79)
Age at diagnosis (yrs)	26.1 (15.55)	29.1 (15.56)	23.7 (11.57)	27.7 (13.73)	25.3 (15.08)	25.5 (15.26)	26.2 (14.31)	26.2 (14.50)
PASI total score	18.99 (5.341)	18.90 (5.272)	19.23 (5.082)	18.46 (5.838)	18.42 (6.873)	20.33 (6.509)	19.07 (5.938)	19.05 (5.831)
IGA score, n (%)								
Severe (4)	5 (11.6%)	13 (30.2%)	7 (16.3%)	8 (19.5%)	8 (18.6%)	12 (28.6%)	48 (22.6%)	53 (20.8%)
Moderate (3)	38 (88.4%)	30 (69.8%)	36 (83.7%)	33 (80.5%)	35 (81.4%)	30 (71.4%)	164 (77.4%)	202 (79.2%)
Previous Psoriasis Medications/Therapies, n (%)								
Phototherapy**	19 (44.2%)	17 (39.5%)	24 (55.8%)	15 (36.6%)	21 (48.8%)	14 (33.3%)	91 (42.9%)	110 (43.1%)
Biologics†	7 (16.3%)	7 (16.3%)	11 (25.6%)	13 (31.7%)	9 (20.9%)	9 (21.4%)	49 (23.1%)	56 (22.0%)
Systemics‡	34 (79.1%)	33 (76.7%)	35 (81.4%)	33 (80.5%)	34 (79.1%)	31 (73.8%)	166 (78.3%)	200 (78.4%)

BID=Twice daily; BMI=Body mass index; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; PsO=Psoriasis; PUVA=Psoralen plus ultraviolet A; QD=Daily; UVB=Ultraviolet B. Data shown are mean (SD), unless otherwise indicated. *Includes all JNJ-77242113 treatment columns. **Includes PUVA or UVB. †Includes etanercept, infliximab, adalimumab, ustekinumab, briakinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, tildrakizumab, alefacept, efalizumab, natalizumab, certolizumab pegol. ‡Includes conventional nonbiologic systemics, novel nonbiologic systemics, 1,25-vitamin D3 and analogues, phototherapy, biologics.

Protagonist Therapeutics

Proportion of Patients Achieving PASI 75 (95% CI) at Week 16



Significant dose-response was detected for PASI 75 at Week 16

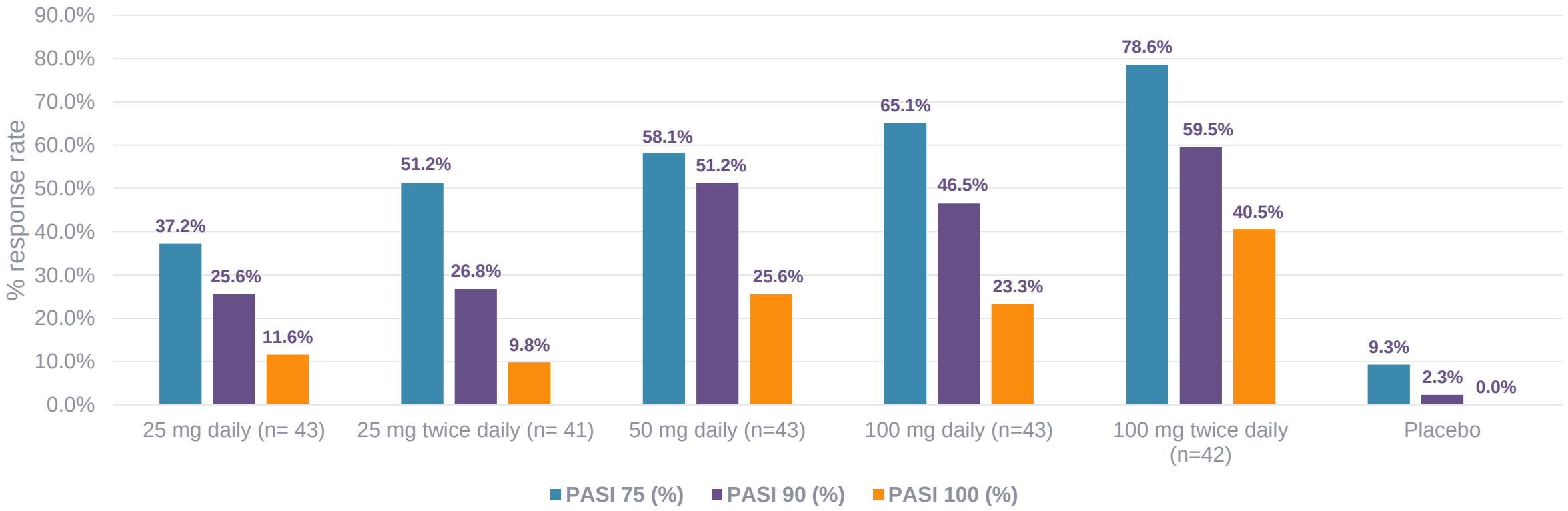
Non-responder imputation

*nominal p <0.001 vs placebo; **nominal p<0.01 vs placebo. p-values are based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline weight category (≤90 kg, >90 kg). Patients who discontinued study agent due to lack of efficacy, worsening of PsO, or use of a prohibited PsO treatment prior to Week 16 were considered non-responders. Patients with missing data were considered non-responders.

Protagonist Therapeutics

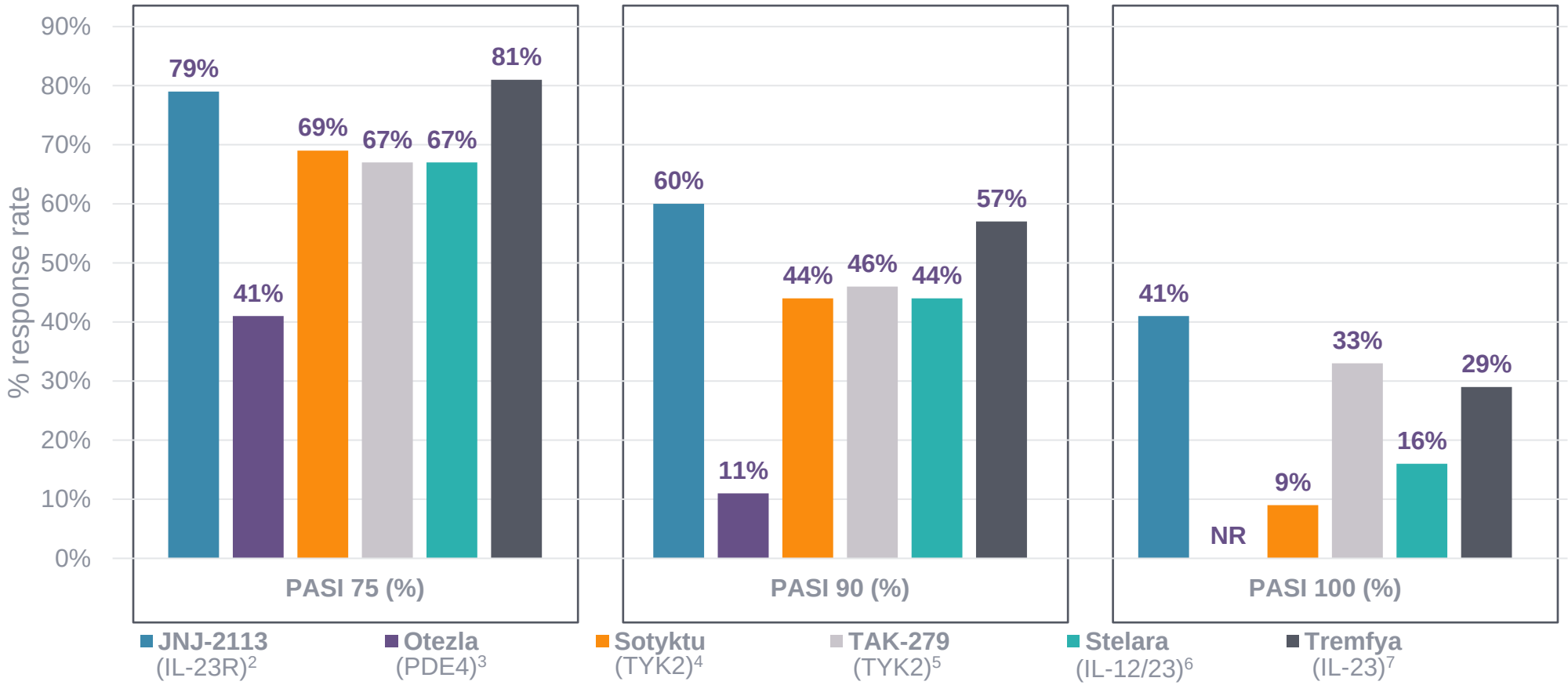
JNJ-2113 Phase 2B Frontier 1 Data

Dose Response



- Clear, linear dose-response
- Once daily dosing appears more efficacious in comparison to twice daily dosing

Cross-Study Comparison of JNJ-2113 to Clinically Relevant Phase 2 Benchmarks[1]



1. Cross trial (not head-to-head) comparisons
2. JNJ2113 100 mg bid dose. Wk 16 endpoint (Placebo: PASI 75: 9.3%, PASI 90: 2.3%, PASI 100: 0%)
3. Otezla 30 mg qd approved dose. Week 16 primary endpoint. Papp K et al. Lancet 2012; 380: 738–46. (Placebo: PASI 75: 5.7%, PASI 90: 1.1%, PASI 100: NR)
4. Sotyktu 3 mg bid dose (6 mg qd dose approved). Wk 12 primary endpoint. Papp K et al. N Engl J Med 2018; 379:1313-1321. (Placebo: PASI 75: 7%, PASI 90: 2%, PASI 100: 0%)
5. TAK-279 30 mg qd dose (Expected phase 3 dose). Wk 12 primary endpoint. AAD 2023. (Placebo: PASI 75: 5.8%, PASI 90: 0%, PASI 100: 0%)
6. Stelara 45 mg wkly x 4 (~approved 90 mg week 0 and 2 approved dose). Wk 12 primary endpoint. Krueger et al. N Engl J Med 2007;356:580-92. (Placebo: PASI 75: 2%, PASI 90: 2%, PASI 100: 0%)
7. Tremfya 200 mg wk 0, 4, then q 8 wks (approved dose 100 mg wk 0, 4 then q 8 wks). Wk 16 primary endpoint. Gordon KB et al. N Engl J Med 2015;373:136-44. (Placebo: PASI 75: 5%, PASI 90: 2%, PASI 100: 0%)

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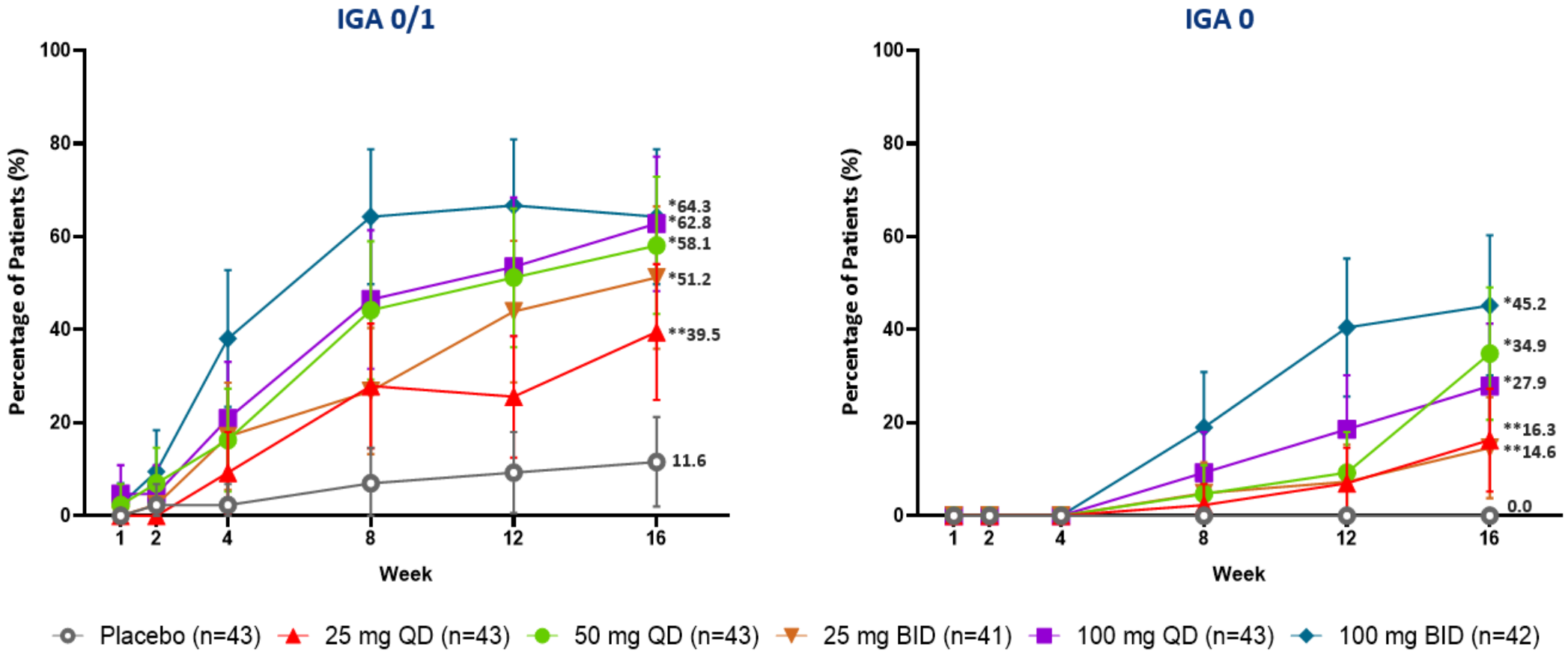
Proportion of Patients Achieving IGA 0/1 and IGA 0 (95% CI) Through Week 16



Non-responder imputation

*nominal p <0.001 vs placebo; **nominal p<0.01 vs placebo. p-values are based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline weight category (≤90 kg, >90 kg). Patients who discontinued study agent due to lack of efficacy/worsening of PsO, or who initiated a prohibited PsO treatment were considered non-responders after the occurrence. Patients with missing data were considered non-responders.

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Number of Patients With ≥1 TEAE With Frequency of ≥5% of Preferred Terms in Any Treatment Group Through End of Study by System Organ Class and Preferred Term

	Placebo	JNJ-77242113					
		25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID	Combined*
Safety analysis set, n	43	43	43	41	43	42	212
Avg duration of follow-up (weeks)	15.03	15.70	15.75	16.20	16.07	15.81	15.90
Patients with ≥1 AE, n (%)	22 (51.2%)	20 (46.5%)	26 (60.5%)	20 (48.8%)	19 (44.2%)	26 (61.9%)	111 (52.4%)
System organ class/Preferred term, n (%)							
Infections and infestations	12 (27.9%)	15 (34.9%)	17 (39.5%)	14 (34.1%)	7 (16.3%)	11 (26.2%)	64 (30.2%)
COVID-19	5 (11.6%)	5 (11.6%)	3 (7.0%)	8 (19.5%)	3 (7.0%)	4 (9.5%)	23 (10.8%)
Nasopharyngitis	2 (4.7%)	1 (2.3%)	8 (18.6%)	3 (7.3%)	1 (2.3%)	2 (4.8%)	15 (7.1%)
Upper respiratory tract infection	1 (2.3%)	3 (7.0%)	0	0	0	2 (4.8%)	5 (2.4%)
Gastrointestinal disorders	5 (11.6%)	3 (7.0%)	6 (14.0%)	4 (9.8%)	4 (9.3%)	7 (16.7%)	24 (11.3%)
Diarrhoea	1 (2.3%)	2 (4.7%)	4 (9.3%)	2 (4.9%)	1 (2.3%)	1 (2.4%)	10 (4.7%)
Nervous system disorders	1 (2.3%)	0	3 (7.0%)	2 (4.9%)	3 (7.0%)	2 (4.8%)	10 (4.7%)
Headache	1 (2.3%)	0	1 (2.3%)	1 (2.4%)	3 (7.0%)	1 (2.4%)	6 (2.8%)
Respiratory, thoracic and mediastinal disorders	1 (2.3%)	1 (2.3%)	1 (2.3%)	0	3 (7.0%)	2 (4.8%)	7 (3.3%)
Cough	0	1 (2.3%)	1 (2.3%)	0	3 (7.0%)	1 (2.4%)	6 (2.8%)

AE=Adverse event; BID=Twice daily; QD=Daily; TEAE=Treatment-Emergent Adverse Events. *Includes all JNJ-2113 treatment columns.
Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.1.

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JNJ-2113 FRONTIER 1 Phase 2b Plaque Psoriasis (PsO) Study

Safety Summary

The proportion of patients experiencing 1 or more AEs was comparable between JNJ-77242113 groups and the placebo group

- Most frequently reported AEs were COVID-19 and nasopharyngitis
- There was no evidence of dose-dependent increase in the occurrence of AEs across the JNJ-77242113 treatment groups

There were three serious AEs that occurred in FRONTIER-1 (n=1 each: suicide attempt, COVID-19, infected cyst; all on active drug and assessed as not related to study intervention by investigators).

No dose-dependent relationship was observed.

A low number of laboratory abnormalities occurred during the study and were comparable between placebo and JNJ-77242113 groups.

There was no evidence of a dose-dependent increase in the occurrence of abnormalities.

There were no deaths, MACE, or malignancies during the study.

JNJ-2113

Conclusions from FRONTIER 1 Phase 2b PsO Study and Next Steps

JNJ-77242113 is a first-in-class oral IL-23R antagonist peptide that demonstrated significantly greater efficacy compared with placebo in patients with moderate-to-severe plaque PsO across all doses in a Phase 2b study

A dose response in PASI scores (75, 90, 100) was demonstrated

JNJ-77242113 was well tolerated at all doses with numbers of AEs comparable to the placebo group. No dose dependent relationship in AEs or lab abnormalities was observed

JNJ-77242113 holds promise as an effective oral therapy with biologic-like efficacy and safety in moderate to severe plaque psoriasis

The FRONTIER 1 results support further development of JNJ-77242113 in phase 3 studies in psoriasis as well as other IL-23 mediated disease indications

Next Steps

- Phase 3 study in psoriasis: expect Janssen to select optimal QD dose, informed by Ph2b results
- Phase 2b study in ulcerative colitis

JNJ-2113 (formerly PN-235) is a potential first, best and only oral IL-23 receptor antagonist

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Janssen SUMMIT Phase 2a Plaque Psoriasis (PsO) Study Design

Delayed Release QD Tablets

Adult Patients with PP

N=90

Eligibility:

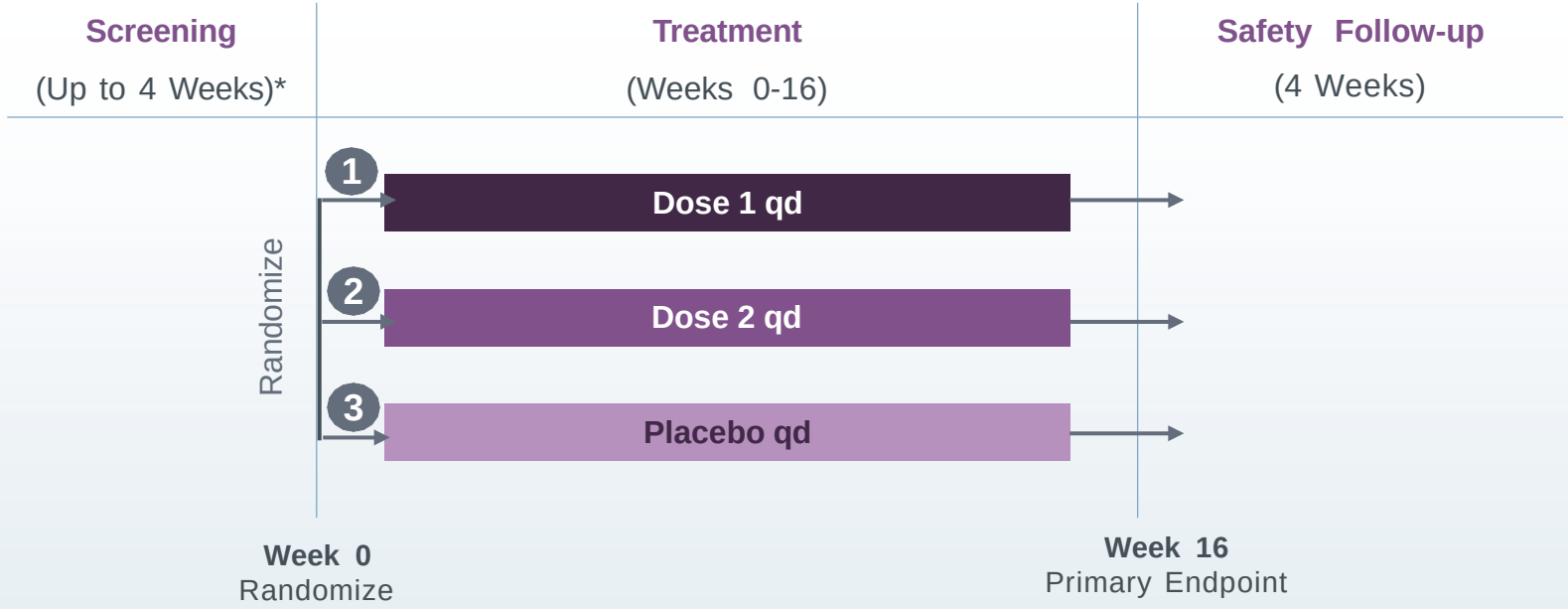
- Moderate – Severe PP

Inclusion:

- BSA ≥ 10%
- PASI ≥ 12

Primary endpoint:

- PASI ≥ 75 at Week 16



Study completed April 10, 2023

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Janssen Milestones Status and Outlook

2023 and Beyond

$112.5m

Upfront and development milestones that have been achieved

$855m

Total future development and sales milestones for which Protagonist remains eligible

Royalty

6% to 10%

- **Upward tiering**
- **10% at >$4B net sales**

Upcoming Potential Milestones		
1st indication	Ph3 initiation	$50M
	Ph3 1° end point achieved	$115M*
	NDA filing	$35M*
	NDA approval	$50M*
2nd indication	Ph2 initiation	$10M
	Ph3 initiation	$15M

* Not included in current cash runway forecast

Protagonist Therapeutics

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Financials

Financial Highlights

Financial Resources Forecast Extends Through Full Year 2025

$230.8M*
+
$108.1M**

CASH & SECURITIES
*as of March 31, 2023
**follow-on offering April 2023

2025

CASH & SECURITIES
provide financial resources forecast through full year 2025[1]

~57.2M

SHARES OUTSTANDING
as of March 31, 2023

[1]Based on our current operating plan and expenditures and including proceeds of the follow-on offering completed in April 2023

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Thank you