Protagonist Therapeutics

COMPANY OVERVIEW

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President & CEO

June 2, 2026

Legal Disclaimer

This presentation and any accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our potential receipt of milestone and royalty payments from J&J and Takeda; market acceptance ICOTYDE™ (icotrokinra); the timing and results of ICOTYDE clinical trials; the commercial potential of rusfertide and other product candidates; our plans for future capital allocation; timing and results related to our pre-clinical and clinical product candidates (including PN-881, PN-477, PN-458 and PN-8047, among others); actions of the U.S. Food and Drug Administration ("FDA") and foreign regulatory agencies, including expectations regarding timing of FDA approval of the NDA for rusfertide; and the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potentially," "predict," "should," "will," or the negative of these terms or other similar expressions.

Forward-looking statements are subject to risks and uncertainties, including those discussed in our filings with the Securities and Exchange Commission, including in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of our most recently filed periodic reports on Form 10-K and Form 10-Q and subsequent filings and in the documents incorporated by reference therein. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. The information included in these materials is provided as of the date specified on the cover page of this presentation, unless specified elsewhere herein, and is qualified as such. Except as required by applicable law, we undertake no obligation to update any forward-looking statements or other information contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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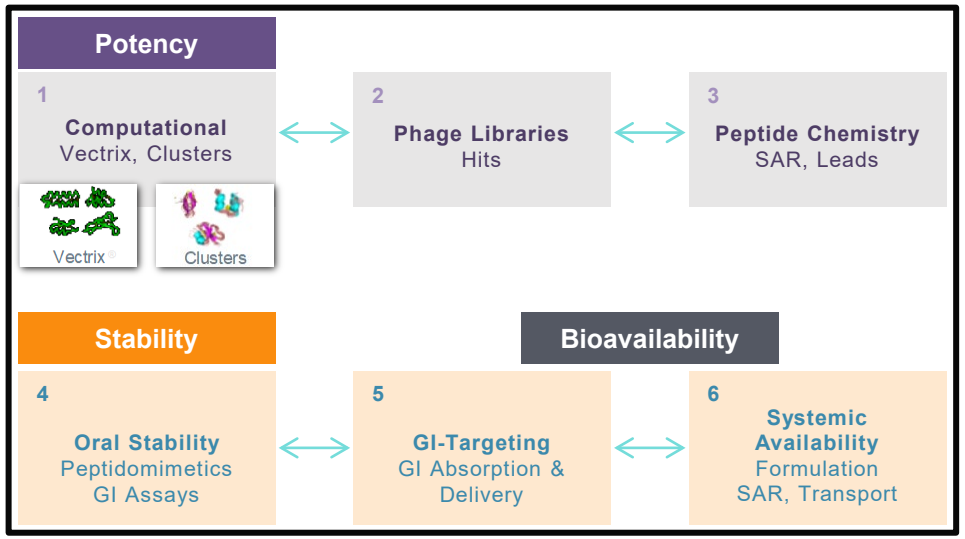
Protagonist's Peptide Technology Platform

Core Competitive Advantage



FDA approved for Plaque Psoriasis

PN-458o
PN-458sc
Dual GLP/GIP

PN-8047
Oral Hepcidin Functional mimetic

PN-477o
Oral Triple Agonist Anti-Obesity

PN-477sc
Weekly sc Triple Agonist Anti-Obesity

PN-881
Oral IL-17 Antagonist

Rusfertide
SC Weekly Hepcidin Mimetic
PV, Ph3
Partner: Takeda

ICOTYDE™
Oral IL-23R Antagonist
Partner: J&J

IND-Enabling

Phase 1

PDUFA Date: PV Q3 '26

Ph 3: PsA, UC, CD

Protagonist Therapeutics

Pipeline: Partnered, Commercial and Near Commercial Assets

ICOTYDE™ and Rusfertide

Programs & Assets	Discovery/Preclinical → IND-Enabling	Phase 1	Phase 2	Phase 3	Key Milestones
INFLAMMATION & IMMUNOLOGY (I&I)					
ICOTYDE (Icotrokinra) Oral IL-23R Peptide Antagonist **Partner:** Johnson & Johnson	**Moderate-to-Severe Psoriasis** ICONIC-LEAD Ph3 completed*, ICONIC-TOTAL Ph3 completed*				★ *ICOTYDE Approved (US) in Plaque PsO Mar '26* • *ICOTYDE in Plaque PsO MAA (EU)* ***submitted*** • *Superiority of icotrokinra vs. deucravacitinib achieved; study of icotrokinra vs ustekinumab completed*
	Psoriatic Arthritis ICONIC-ADVANCE-1&2 Ph3 completed*, ICONIC-ASCEND Ph3 completed*				
	Ulcerative Colitis ICONIC PsA-1 & -2 Ph3 ongoing				
	Crohn's Disease ANTHEM-UC Ph2b completed*; ICONIC-UC Ph3 initiated				• *ICONIC-UC initiated* ***Q4 '25***
	ICONIC-CD Ph 2/3 initiated				• *ICONIC-CD initiated* ***Q4 '25***
HEMATOLOGY					
Rusfertide Subcutaneous Hepcidin Mimetic **Partner:** Takeda	**Polycythemia Vera** REVIVE Ph2 completed**, THRIVE Ph3 ongoing, PACIFIC Ph2 completed**, VERIFY Ph3 completed*				• *NDA: Submitted 29 Dec '25; priority review granted Mar '26;* ***PDUFA Date Q3 '26***

*Primary endpoint completed; **Study completed.

Pipeline: Wholly Owned Assets and Programs

PN-881, PN-8047, PN-477o & PN-477sc, PN458o & PN458sc

Programs & Assets	Discovery/Preclinical → IND-Enabling	Phase 1	Phase 2	Phase 3	Key Milestones
I & I	**PN-881** Oral IL-17 Antagonist	**Psoriasis, Psoriatic Arthritis, Hidradenitis Suppurativa, Spondyloarthritis** Ph2 planned Ph1 initiated			• *Phase 2 PsO initiation **Q4 '26*** • *Phase 1 initiated in **Q4 '25***
HEMATOLOGY	**PN-8047** Oral Hepcidin	**Polycythemia Vera, Hereditary Hemochromatosis, Other** IND-Enabling Studies		*Phase 1 Clinical PoC*	• *DC: Nominated in **Q4 '25***
METABOLIC	**PN-477sc and oral** GLP-1R, GIPR, and GCGR Agonist **PN-458sc and oral** GLP-1R and GIPR Agonist	**Obesity & Associated Co-Morbidities** IND-Enabling Studies IND-Enabling Studies IND-Enabling Studies IND-Enabling Studies		*Phase 1 Clinical PoC*	• *PN-477sc Phase 1 initiation **Mid '26*** • *PN-477o Phase 1 initiation **Q1 '27*** • *PN-458sc DC: Nominated **Q4 '25*** • *PN-458o DC: Nominated **Q4 '25***

DC, Development Candidate; PsO, Plaque Psoriasis.

Multiple Near-Term Catalysts

Two Potential Blockbuster Approvals, Multiple R&D Readouts & Strong Cash Position

Commercial Value Drivers

- ***ICOTYDE:*** First-in-class oral IL-23R antagonist
  - Partner: Johnson & Johnson
  - US FDA approval for plaque psoriasis: Mar ‘26 ✓
  - MAA submitted Sep ‘25
  - 3 additional indications
- ***Rusfertide:*** First-in-class hepcidin hormone mimetic
  - Partner: Takeda
  - NDA submitted for PV: Dec ’25; Priority Review granted: Mar ’26; PDUFA Date: Q3 ‘26

Multiple Clinical Programs I&I, Obesity and Hematology

I & I

- ***PN-881:*** Oral IL-17 antagonist
  - Ph1 in progress[1]

Heme

- ***PN-8047:*** Oral hepcidin functional mimetic
  - IND enabling studies

Obesity

- ***PN-477sc & PN-477o:*** Triple-G, weekly sc and daily oral
  - Ph1 initiation (sc) in mid ’26
- ***PN-458sc & PN-458o:*** Dual GLP-1R/GIPR agonist
  - IND-enabling studies

Next Wave of Active Discovery Programs

Lead optimization/Pre-clinical:

- **IL-4Rα** oral antagonist
- **Amylin** oral mono/poly-agonists
- Other programs

Strong Cash Position

- Fund internal, fully-owned programs to clinical PoC
- Capital return to shareholders – consider share buybacks

1. Clinicaltrials.gov. NCT07153146.

Protagonist Therapeutics

Protagonist Therapeutics

Business Overview

- **Commercial and Late-Stage Assets**
  - ICOTYDE™
  - Rusfertide
- **De-risked Strategy and Strengthened Pipeline**
  - De-risked targets (IL-17, hepcidin, obesity)
  - Validated platform and approach (ICOTYDE, rusfertide)
- **Accelerated Path to Clinical Proof of Concept (PoC)**
  - Phase 1 PoC planned for obesity and oral hepcidin programs
  - Well-established clinical PoC pathway in I&I programs
- **Non-Dilutive Funding Model**
  - $620M cash (1Q26); Additional opt-out, milestones, and royalty payments expected by year-end
  - Royalty streams from ICOTYDE (6–10%) and rusfertide (14–29%), plus milestone payments
  - No planned equity raise in the foreseeable future
  - Potential share buyback program announcement by year-end

ICOTYDE (Icotrokinra)

J&J and Protagonist Collaboration Economics

- **$387.5M: Upfront + milestones achieved to-date**

- **$580M: Future potential development, regulatory and sales milestones**
  - $155M development & regulatory milestones achievable by 2028-29
  - $425M sales milestones with highest hurdle at $5 billion yearly net sales

- **6%-10% tiered royalties**
  - 7.25% weighted average at $4B annual sales
  - 10% for annual sales ≥$4B

Illustrative royalties in peak sales year				
Annual net sales*	$5.0B	$10.0B	$15.0B	$20.0B
Pre-tax royalty receivable*	$0.4B	$0.9B	$1.4B	$1.9B

*Sensitivity analysis purposes only and does not represent management guidance, expectations or projections

Rusfertide

Takeda and Protagonist Partnership Economics

- **$325M: Upfront + milestones achieved to-date**

- **$950M: Future potential development, regulatory and sales milestones**
  - $175M development & regulatory milestones
  - $775 sales milestones with highest hurdle at $2.5 billion yearly net sales

- **$400M: Opt-out fee**
  - $200M payable upon opt-out (April ‘26)
  - $200M upon FDA approval

- **14%-29% tiered royalties**
  - 21% weighted average at $1.5B annual sales
  - 29% for annual sales ≥ $1.5B

Illustrative royalties during peak sales year (Opt-out Scenario)				
Annual net sales*	$1.0B	$1.5B	$2.5B	$3.5B
Pre-tax royalty receivable*	$0.2B	$0.3B	$0.6B	$0.9B

*Sensitivity analysis purposes only and does not represent management guidance, expectations or projections

Protagonist Therapeutics

ICOTYDE™ (Icotrokinra; JNJ-2113, formerly PN-235): Oral IL-23 Receptor Antagonist Peptide

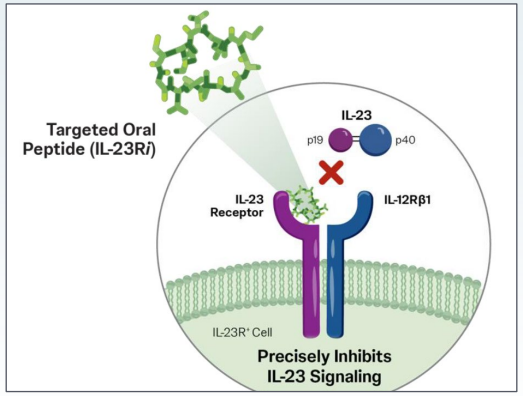
Setting a new standard of treatment in plaque psoriasis & other IL-23 mediated diseases

J&J Partnership: 2017 to Present

ICOTYDE (Icotrokinra): First Oral IL-23R Therapy Targeting a >$80B[1] Market

THE INNOVATION

- ***First- and only-in-class ORAL*** IL-23R antagonist in late-stage development
- **Four major indications:**
  - Psoriasis (PsO)
  - Psoriatic arthritis (PsA)
  - Ulcerative colitis (UC)
  - Crohn's disease (CD)



Abreu et al., UEG Week, October 7, 2025, Berlin – OP206

THE OPPORTUNITY

Stelara®	>$11B[2]
Tremfya®	>$10B[3]
Skyrizi®	>$20B[4]

~90% *of patients receiving SC/IV therapy and willing to switch to an oral option with comparable safety and efficacy*[5]

PsO / IBD patients eligible for advanced therapies but remaining untreated[6] ▶ **~50-70% (5M)**

>$10B[7] blockbuster potential

Biologic-like efficacy and safety, with convenience of a once-daily pill

1. Evaluate 2030 projected market size for PsO, PsA, IBD, UC.
2. J&J reported sales in 2023 (peak year).
3. J&J Q2 earnings call, July 17, 2025.
4. Abbvie Full-year and Q4 2024 financial results, Jan 31, 2025.
5. Stein Gold L, et al., Presented at 2025 Fall Clinical Dermatology Conference, Oct 2025, Las Vegas, NV.
6. J&J remarks, Enterprise Day Presentation, Dec 2023.
7. HSBC Dec 2025 Consensus Forecast.

Protagonist Therapeutics

FDA Approved in March 2026: **ICOTYDE™**

ICOTYDE is the first and only targeted oral peptide that blocks the IL-23 receptor

Protagonist Therapeutics

Protagonist Therapeutics Announces U.S. FDA Approval of ICOTYDE(TM) (icotrokinra) for the Treatment of Moderate to Severe Plaque Psoriasis

Wednesday, 18 March 2026 08:05 AM

Topic: Company Update

ICOTYDE is the first and only IL-23R targeted oral peptide that delivers complete skin clearance and a favorable safety profile in a once-daily pill

Approval supported by four phase 3 studies that met all primary endpoints and demonstrated a favorable safety profile in 2,500 patients

$50 million milestone payment triggered by FDA approval; Protagonist is eligible to receive 6 - 10% royalties on sales and up to $580 million in future milestone payments

Webcast and conference call to be held at 8:30 am ET on March 18

ICOTYDE™

US FDA approval of ICOTYDE™, formerly PN-235, for treatment of moderate-to-severe plaque psoriasis

- Johnson & Johnson partnership overview
  - 2017 to present
  - Protagonist completed pre-clinical and first Ph1 study[1]
  - J&J responsible for further development and commercialization

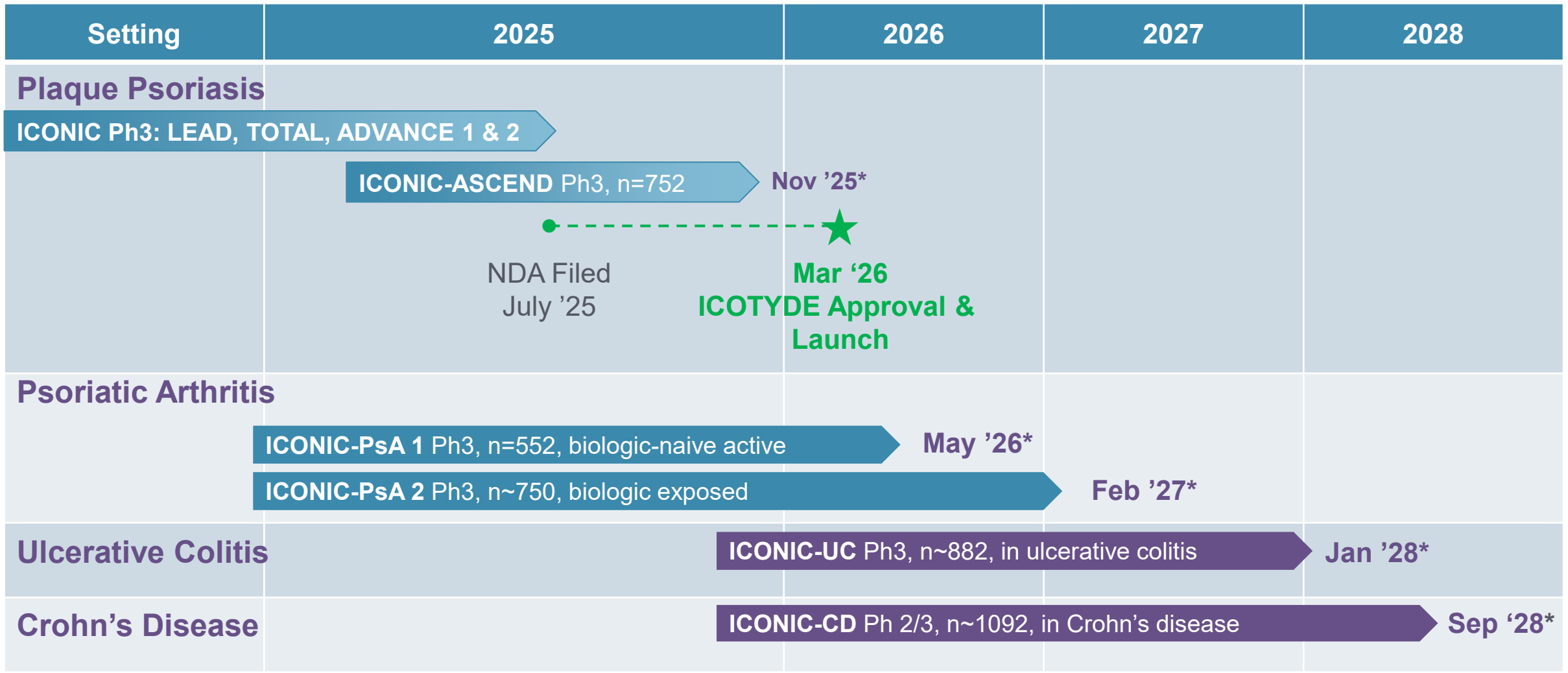
- ICOTYDE is the first and only IL-23R targeted oral peptide to
  - deliver injectable biologics-like skin clearance, with
  - a favorable safety profile (ie, no mandatory TB test or lab monitoring), and
  - the convenience of a once-daily pill

- Approval supported by four phase 3 studies that met all primary endpoints and demonstrated a favorable safety profile in 2,500 patients

1. Fourie, AM et al. JNJ-77242113, a highly potent, selective peptide targeting the IL-23 receptor, provides robust IL-23 pathway inhibition upon oral dosing in rats and humans. *Sci Rep* 2024(14):17515. https://doi.org/10.1038/s41598-024-67371-5.

ICOTYDE Approved in Moderate-to-Severe Plaque Psoriasis (Mar'26)

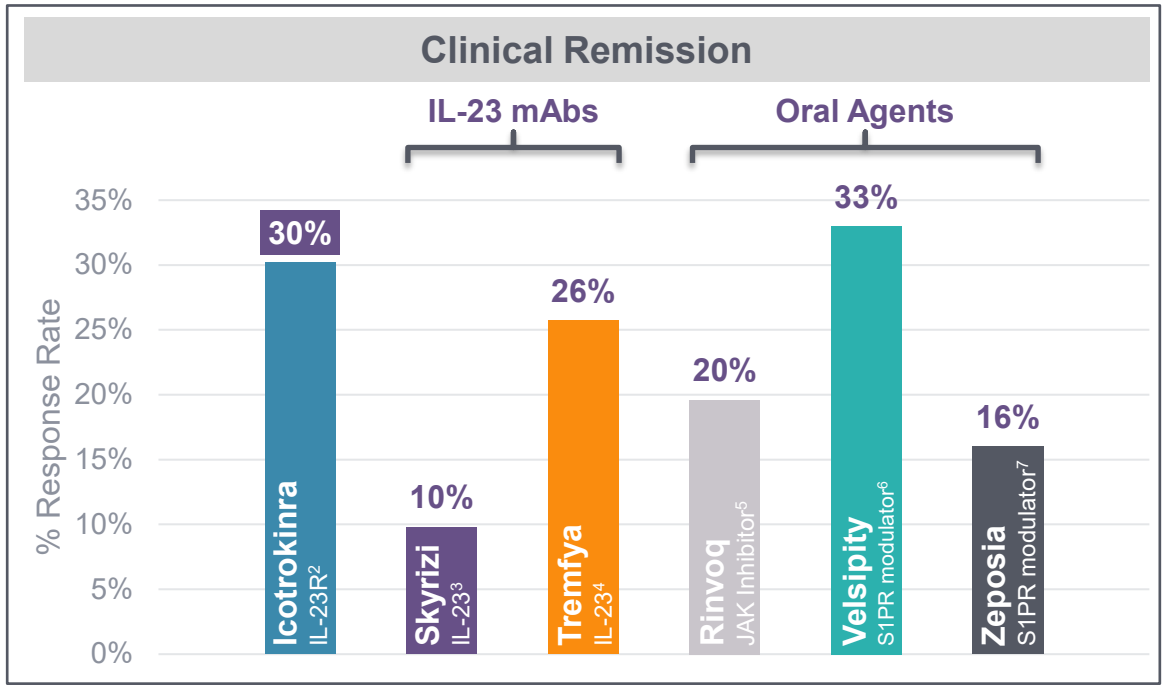
Potential Expansion of Multiple Indications in Coming Years



* Primary Completion Date on clinicaltrials.gov

Icotrokinra Cross-Trial Comparison to Phase 2 Benchmarks in UC[1]

Clinical Remission



Agent	Endpoint Timeframe	Placebo Remission (%)
Icotrokinra	**Wk 12**	**11.1**
Skyrizi	Wk 12	1.7
Tremfya	Wk 12	9.5
Rinvoq	Wk 8	0
Velsipity	Wk 12	8.1
Zeposia	Wk 8	6

1. Cross trial (not head-to-head) comparisons of unadjusted (ie, non-placebo adjusted) remission data from phase 2 studies.
2. Icotrokinra (JNJ-2113) highest dose (in mg; PO qd) with clinical remission at Wk 12 (ie, Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy). Clinical remission (placebo): 11.1%. Protagonist Therapeutics, Inc. "Protagonist Reports Positive Top Line Results from Phase 2b Study of Icotrokinra Showing Potential to Transform the Treatment Paradigm for Patients with Ulcerative Colitis." News release. 10 March 2025.
3. Skyrizi 1200 mg IV (approved dose; phase 2 data) clinical remission per Adapted Mayo score at Wk 12 (ie, stool frequency subscore ≤1, and not greater than baseline, rectal bleeding subscore =0, and endoscopic subscore ≤1 without the evidence of friability). Clinical remission score (placebo): 1.7%. Louis E, et al., *JAMA*. 2024;332:881-97.
4. Tremfya 200 mg IV (approved dose; phase 2 data) clinical remission at Wk 12 (ie, Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a Mayo rectal bleeding subscore of 0, and a Mayo endoscopy subscore of 0 or 1 with no friability present on endoscopy). Clinical remission (placebo): 9.5%. Peyrin-Biroulet L, et al., *Gastroenterology*. 2022;165:1443-57.
5. Rinvoq 45 mg PO QD (approved dose; phase 2 data) with clinical remission at Wk 8 (ie, adapted Mayo score; defined as stool frequency subscore of 1, rectal bleeding subscore of 0, and endoscopic subscore of 1). Clinical remission (placebo): 0%. Sandborn WJ, et al., *Gastroenterology*. 2020;158:2139-49.
6. Velsipity 2 mg PO QD (approved dose; phase 2 data) with clinical remission at Wk 12 (ie, Mayo Clinic endoscopic subscore ≤1 [with absence of friability], rectal bleeding score ≤1, and stool frequency score ≤1, with a frequency decrease of ≥1 point from baseline). Clinical remission (placebo): 8.1%. Sandborn WJ, et al., *Gastroenterology*. 2020;158:550-61.
7. Zeposia 1 mg PO QD (approved dose; phase 2 data) with clinical remission at Wk 8 (ie, Mayo Clinic score ≤2, with no subscore >1). Clinical remission (placebo): 6%. Sandborn WJ, et al., *New Engl J Med*. 2016;18:1754-62.

Protagonist Therapeutics

Icotrokinra Phase 3 Ulcerative Colitis (ICONIC-UC) and Phase 2b/3 Crohn's Disease (ICONIC-CD) Clinical Studies

Potential Registration-Enabling, Phase 3 Studies Underway

- **Phase 3 ICONIC-UC study in adult and adolescent participants with moderately to severely active ulcerative colitis[1]:**
  - Double-blind induction study in adults (co-primary endpoint at Week 12):
    - Percentage of adult participants in clinical remission[a]
  - Double-blind maintenance study in adults (co-primary endpoint at Week 40):
    - Percentage of adult participants in clinical remission[a]
  - Open-label induction study in adolescents (endpoint at Week 12):
    - Percentage of adolescent participants in clinical response[b]
  - Open-label maintenance study in adolescents (co-primary endpoint at Week 40):
    - Percentage of adolescent participants in clinical remission[a]
- **Phase 2/3 ICONIC-CD study in participants with moderately to severely active Crohn's disease[2]:**
  - Induction study 1 (co-primary endpoint at Week 12):
    - Number of adult participants with clinical response[c]
  - Induction study 2 (co-primary endpoint at Week 12):
    - Number of adult participants with clinical remission[d]
    - Number of adult participants with endoscopic response[e]
  - Maintenance study in week 12 induction responders with co-primary endpoints at Week 40:
    - Number of adult participants with clinical remission[d]
    - Number of adult participants with endoscopic response[e]

[a]Clinical remission is defined as stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0/1.
[b]Clinical response defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0/1.
[c]Clinical response is defined as ≥100-point reduction from baseline in Crohn's Disease Activity Index (CDAI) score. CDAI scores range from 0 to approximately 600. Higher score indicates higher disease activity.
[d]Clinical remission is defined as CDAI score <150. CDAI scores range from 0 to approximately 600. Higher score indicates higher disease activity.
[e]Endoscopic response is defined as >50% improvement from baseline in Simple Endoscopic Score for Crohn's Disease (SES-CD) score or a decrease of at least 2 points in participants with a baseline score of 4 and isolated ileal disease. SES-CD score can range from 0 to 56. Higher scores indicate more severe disease.

Protagonist Therapeutics

1. ClinicalTrials.gov. NCT07196748. Accessed on 30 September 2025.
2. ClinicalTrials.gov. NCT07196722. Accessed on 30 September 2025.

Protagonist Therapeutics

Rusfertide: Hepcidin Mimetic Potential as a New Practice Changing Standard of Care in Polycythemia Vera (PV)

PV: A rare myeloproliferative neoplasm characterized by excessive production of red blood cells[1]

- Primary treatment goal is to maintain Hct <45%[2,3,4]

Polycythemia Vera. 1. 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. 4. Barbui, T, et al. *Leukemia* 2018;32;1057-69.

Polycythemia Vera (PV)

Significant Unmet Medical Need

1. Hct Control

- **Maintaining Hct<45% is critical,** as per NCCN guidelines
- **~4 times higher risk of death from uncontrolled Hct**[1]

2. Patients

- Up to **78% of patients have uncontrolled Hct** ≥45%[2]
- **Thrombotic events (34-41%)**[3-5]
- **Burdensome symptoms**
  - Fatigue within last 12 months (73%)[6]
  - Full days in bed (23%)[6]
  - Iron deficiency (anemia)[7]

3. Therapy

- **Current standard of care (SOC)**
  - Phlebotomy, hydroxyurea (HU), interferon, Jakafi
  - Inadequate
- No **RBC-specific pharmaceutical option** available

Rusfertide, a hepcidin mimetic, could potentially provide a RBC-specific treatment option for PV

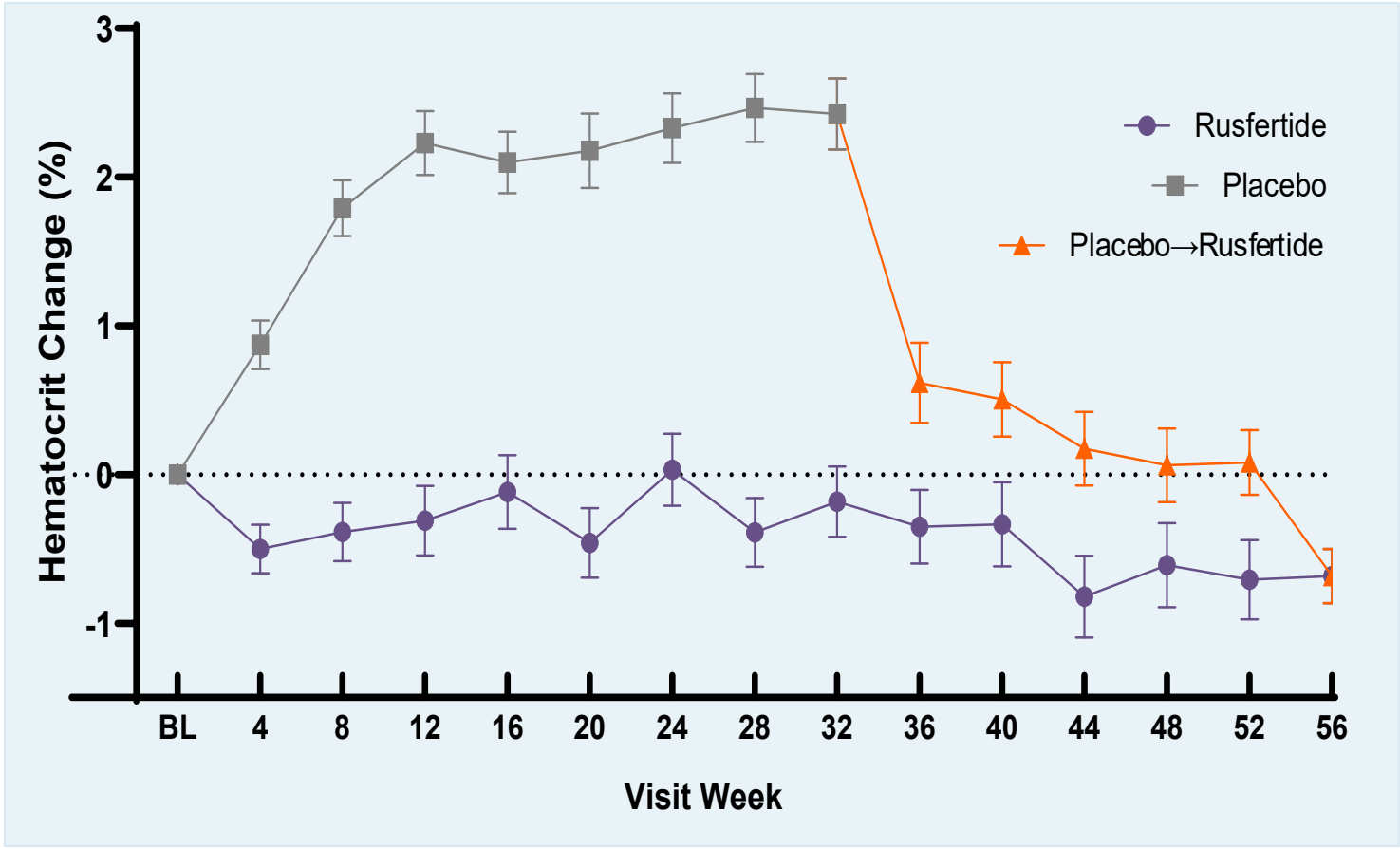
1. Marchioli R, et al. *N Engl J Med.* 2013;368:22-33.
2. Verstovsek S, et al. *Ann Hematol.* 2023;102(3):571-581.
3. Kaifie A, et al. *J Hematol Oncol.* 2016;9:18.
4. Griesshammer M, et al. *Ann Hematol.* 2019;98(5):1071-1082.
5. Polycythemia vera: the natural history of 1213 patients followed for 20 years. Gruppo Italiano Studio Policitemia. *Ann Intern Med* 1995;123(9):656-64.
6. Mesa R, et al. *BMC Cancer* 2016;16:167.
7. Ginzburg et al. *Leukemia* 2018;32:2105-2116.

Rusfertide Phase 3 VERIFY Study Results: PV[1,2]

Durable, Sustained Hct Control With Fewer PHLs vs. Placebo, Addressing Major Unmet Need in PV[1,2]

- **Primary endpoint:** Wks 20-32
  1. Clinical Response: rusfertide vs placebo ($p<0.0001$) ✓
- **Key 2° endpoints:** Wks 0-32
  1. Average number of PHLs ($p<0.0001$) ✓
  2. Proportion of patients with Hct <45% ($p<0.0001$) ✓
  3. Average PROMIS Fatigue SF-8a Score ✓
  4. Average MFSAF Total Symptom Score ✓

Rusfertide was generally well-tolerated through 52 Weeks of treatment. The most common treatment-emergent adverse events (AE) in rusfertide-treated patients were injection site reactions (47.4%), anemia (25.6%) and fatigue (19.6%), which were primarily grade 1 or 2. Serious AEs occurred in 8.1% of overall rusfertide-treated patients.



VERIFY featured in **Plenary Presentation** at ASCO'25

Protagonist Therapeutics

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

1. Kuykendall AT, et al. *J Clin Oncol* 2025;43(LBA3); 2. Kuykendall AT, et al. *Blood* 2025;146(Suppl 1):81.

Rusfertide: An RBC-Centric Treatment Option for PV

Peak Revenue Potential of $1-2 Billion[3]

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

Treatment Paradigm

Patients are often on polytherapy and will cycle through various treatments[1]

~41k Phlebotomy (PHL) — And/Or — **~26k** Hydroxyurea (HU) — And/Or — **~6k** Ruxolitinib — And/Or — **~3k** Ropeg-interferon

- Unmet need exists at each step of the treatment landscape
  - **~78% with uncontrolled Hct<45% despite current treatments[2]**
- **Rusfertide expected to be used at each step[3]**

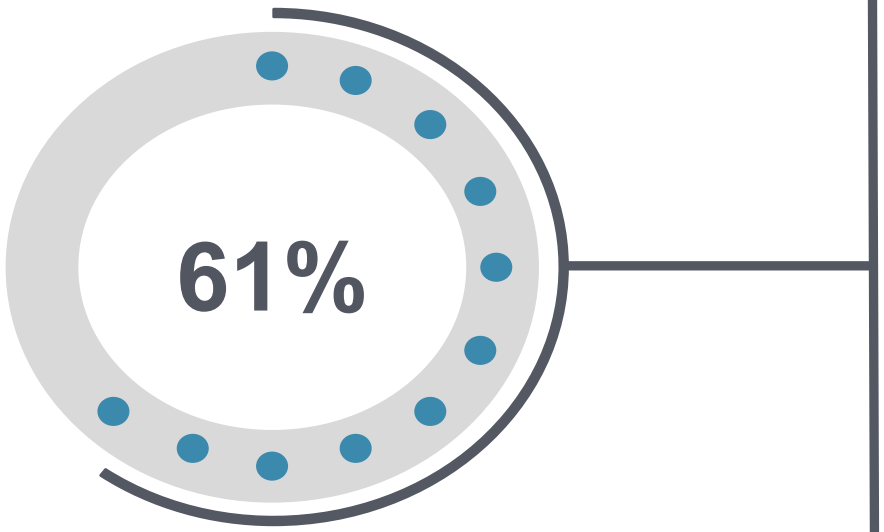
Rusfertide provides consistent hematocrit control and can potentially reduce treatment burden to achieve **peak revenue potential of $1-2B[3]**

1. Komodo Health closed claims dataset (2016-2023); Note: ~2,000 patients are treated via a combination of other therapies.
2. 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
3. Takeda FY2025 Q2 Earnings Release.

Protagonist Therapeutics

Most Patients With Polycythemia Vera Experience Suboptimal Hct Control

Frequent Phlebotomies, High-Dose Hydroxyurea and/or Post-Treatment TEs Are Common



Regimens among patients with PV who received burdensome treatment and/or experienced a TE (N=27,116)[1]

54% **Frequent phlebotomies (PHLs)**
Patients receiving ≥3 PHLs in 6 months

28% **High-dose hydroxyurea (HU)**
Patients receiving ≥1,000 mg HU per day

8% **Combination of PHL and HU**
Patients receiving a combination of frequent phlebotomies and high-dose HU

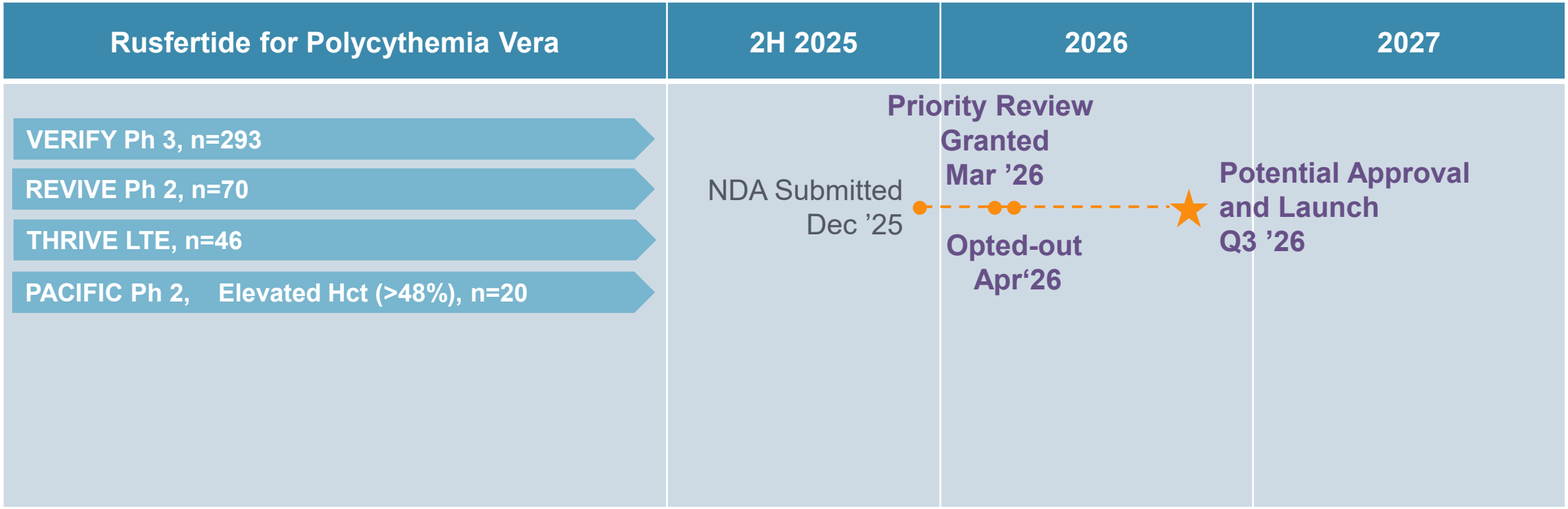
Komodo Health claims database (data from January 2016 to December 2022); includes patients who were ≥18 years old and had at least two clinical diagnoses of PV that were at least 6 months apart.

1. Kuykendall A, et al. *Expert Rev Hematol*. 2025;Epub ahead of print.

Protagonist Therapeutics

Rusfertide for PV: NDA Filing, Approval and Commercialization Launch Timelines

FDA Granted Rusfertide NDA Priority Review in March 2026



Rusfertide has **Orphan Drug** designation, **Fast Track** status, and **Breakthrough Therapy** designation

Potential FDA approval and commercial launch in Q3 2026

Protagonist Therapeutics

Protagonist Therapeutics

R&D Pipeline
I&I, Hematology, Obesity

PN-881:
Oral IL-17 Peptide Antagonist

Clinically and commercially validated target
for multiple inflammatory conditions

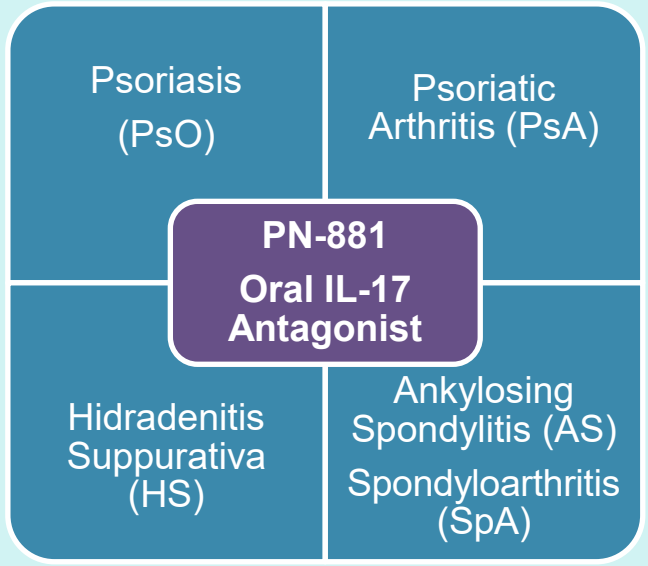
Targeting a $17B+ Market Opportunity with Differentiated ORAL IL-17 Inhibition

PN-881: A Potential Best-in-Class Oral IL-17A and F Antagonist

IL-17: Validated Market Opportunity[1]

- ***31% of PsO market*** by 2031
- ***$17B+ opportunity*** **currently** dominated by injectables

Strategic Indication Expansion



PN-881: Differentiated Target Product Profile

PN-881 Blocks All Three IL-17 Dimers

- ***Oral Peptide***
- ***Triple specificity***[2] matching Bimzelx profile
- Potential ***best-in-class profile***

PN-881: A wholly-owned **ORAL** IL-17A and F antagonist in Clinical Studies

Protagonist Therapeutics

1. Psoriasis Disease Landscape and Forecast (Clarivate, 2023); Evaluate sales data
2. Blockade of both IL-17A and IL-17F leads to greater efficacy. Reich et al., N Engl J Med 2021;385:142-52. DOI: 10.1056/NEJMoa2102383

Criteria for Nomination of Oral PN-881 Development Candidate[1]

Oral PN-881 Achieved all the Criteria for a Development Candidate Nomination

Attribute	Criteria
Potency	✓ Sub-nM potency *vs.* IL-17 AA ✓ Blocks all dimeric forms of IL-17: AA, AF, FF
Stability	✓ Stable in simulated gastric and intestinal fluids ✓ Stable in serum with $t_{1/2}$ >24 hr ✓ Metabolic stability ✓ Thermostability
PK	✓ Oral exposure and half-life in rodent and higher species sufficient for oral daily dosing
PD model	✓ Mouse hIL-17 challenge, CXCL1 model
Efficacy Model	✓ Rat IL-23-induced skin inflammation model

Protagonist Therapeutics

1. Manrique M, et al. Presented at the European Academy for Dermatology and Venereology (EADV) Congress. September 17-20, 2025, Paris, France.

PN-881 Potently Inhibits IL-17AA, AF, and FF[1]

Similar Potency to Bimekizumab and ~70-fold More Potent Than Secukinumab

PN-881 vs Injectables	Neonatal Human Dermal Fibroblast (nHDF) and Human HT-1080 Fibrosarcoma Cell Line (HT-1080) IC_{50} (nM)					
	IL-17 AA		IL-17 AF		IL-17 FF	
	nHDF	HT-1080	nHDF	HT-1080	nHDF	HT-1080
PN-881 (Oral)	**0.15**	**0.13**	**29**	**27**	**15**	**14**
Injectable Agents						
Bimzelx®	0.12	0.17	18	19.5	14	13
Cosentyx®	10	11	175	151	Inactive	Inactive

ND, not determined.

1. Adapted From Manrique M, et al. Presented at the European Academy for Dermatology and Venereology (EADV) Congress. September 17-20, 2025, Paris, France.

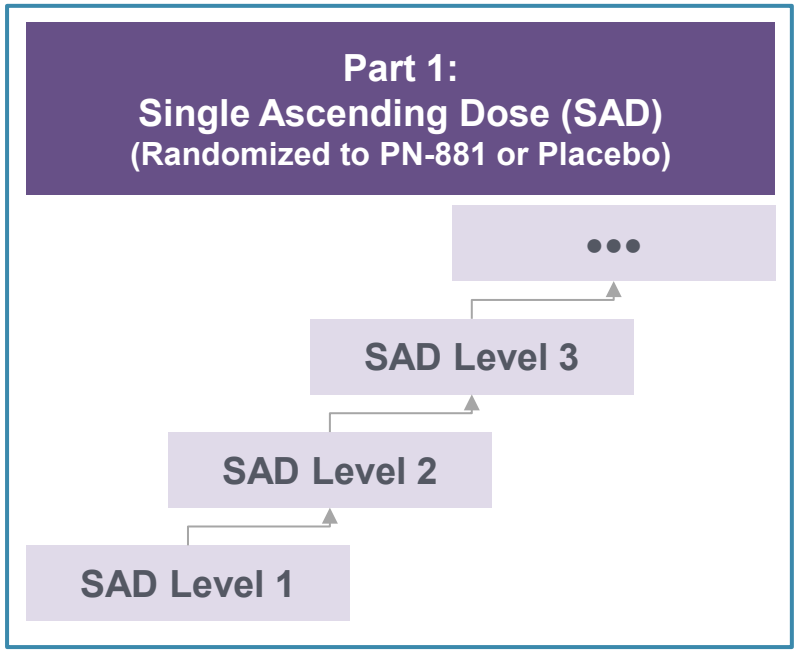
PN-881 Achieves Desired Pharmacology in Preclinical Models

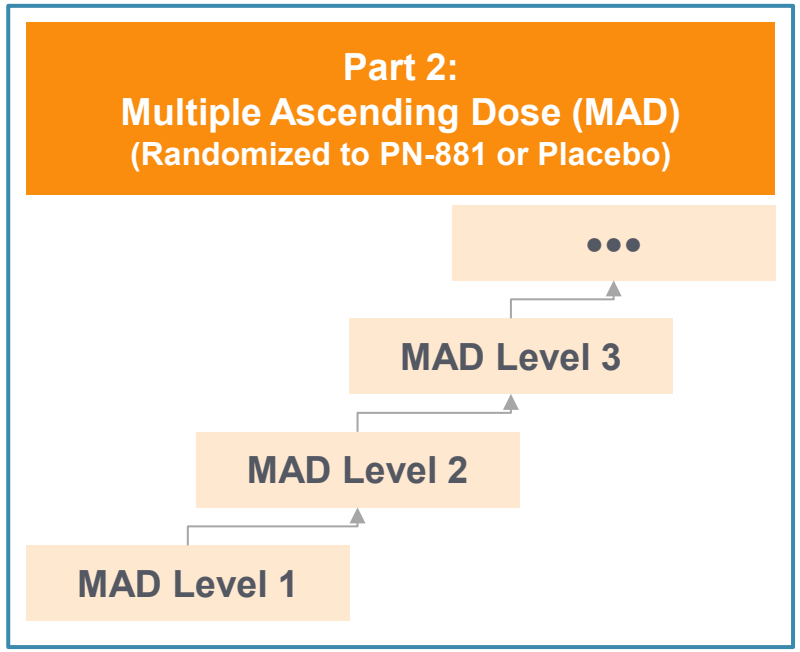
- High systemic exposures after oral administration to mice, rats, dogs, and cynomolgus monkeys
  - >100 ng/mL in cynomolgus monkeys with oral dose of 2.5 mg/kg

- Blockade of IL-17 in in vivo mouse models after oral administration
  - PN-881 inhibits CXCL1 production in serum and in skin in mice challenged with supra-physiologic doses of human IL-17
  - PN-881 shows efficacy at doses as low as 1 mg/kg BID in inhibiting ear inflammation (erythema and thickness) in rats challenged with repeated IL-23 injections

- Suitable tissue distribution into the skin in preclinical models
  - Ratio of skin-to-plasma concentrations comparable to or better than monoclonal antibodies

PN-881: Comprehensive Phase 1 Study in Healthy Human Volunteers (N~142)





Part 3:
Assessment of Solid Dose Formulations

Part 4:
Effect of Food on Solid Dose Formulation

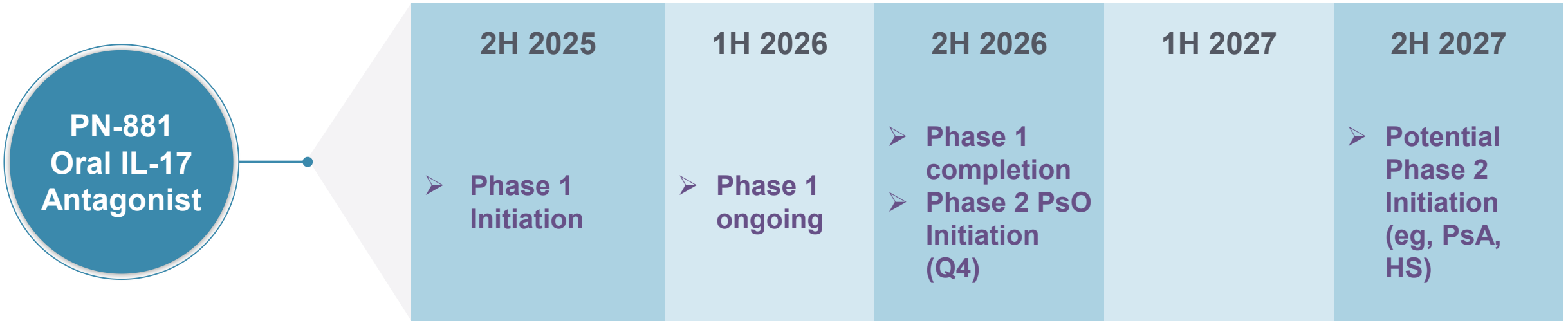
Part 5:
Multiple Dose PK of Solid Dose Formulation

- **Primary endpoint:**
  - Incidence and severity of treatment-emergent adverse events (pre-dose to 7 days after last dose)
- **Secondary endpoints:**
  - Pharmacokinetics and pharmacodynamics

Phase 1 completion by mid-year; Phase 2 Plaque Psoriasis study initiation by year end

Protagonist Therapeutics

PN-881: Near-Term Clinical Development Plan



HS, hidradenitis suppurativa; PsO, plaque psoriasis.

Protagonist Therapeutics

PN-8047: An Oral Hepcidin Functional Mimetic

Working towards a Hepcidin pathway based ORAL option in erythrocytosis mediated indications

PN-8047: Oral Hepcidin Functional Mimetic

Leverages Our Expertise in the Hepcidin Pathway

Rusfertide established hepcidin mimetics as a therapeutic option for polycythemia vera

Clinical validation of hepcidin biology

PN-8047: a wholly owned asset that builds on Protagonist's knowledge base of hepcidin pathway

Novel oral small molecule; selected from extensive head-to-head comparison of different modalities

Potentially maximizes the total addressable global market for hepcidin mimetics

Provides a therapeutic option that may reduce treatment barriers

New IP provides extended periods of market exclusivity

Protagonist Therapeutics

PN-8047: An Oral Hepcidin Functional Mimetic for Targeting Polycythemia Vera

PN-8047 has similar potency as rusfertide and is superior to hepcidin

	Human-FPN Potency EC_{50} (nM)
Hepcidin	13.7
Rusfertide	2.5
PN-8047	**4.3**

Table shows average values for effective concentration for 50% signal (EC_{50}) in nano-molar (nM)
Human-FPN assay measured functional response of increases in transferrin-receptor1 due to increase in intracellular iron concentrations after ferroportin internalization
Cyno-FPN assay measured reduction in NanoLuc® Luciferase signal, downstream of ferroportin internalization

FPN, Ferroportin; Cyno, Cynomolgus Monkey

Protagonist Therapeutics

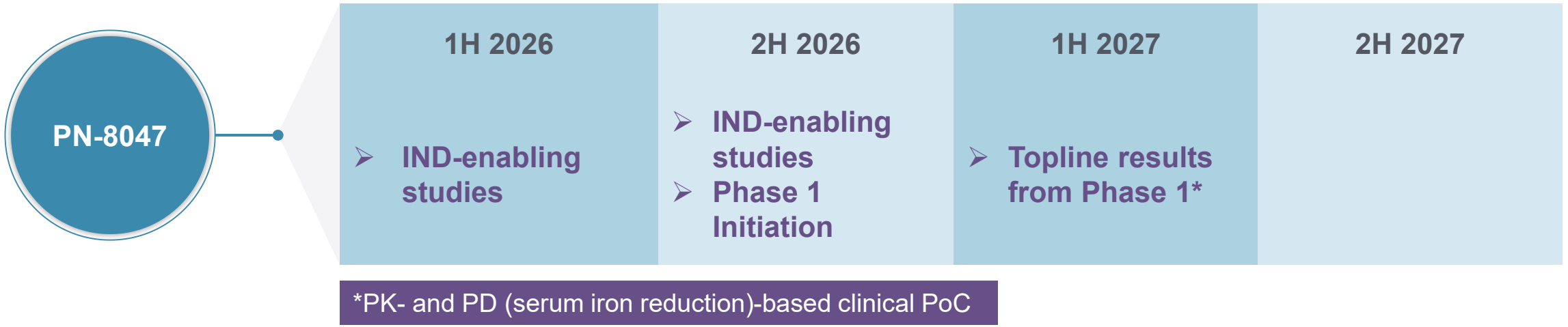
PN-8047: Novel Oral Small Molecule that is Potent with Excellent PK, PD, and Efficacy Properties

Attributes	Summary of PN-8047 Properties
Potency	✓ Nanomolar potency in the T47D-TfR1 functional assay ✓ Similar potency as Rusfertide
in vitro ADME	✓ Metabolically stable in liver microsomal incubations ✓ Good permeability for oral dose
PK	✓ Oral exposure and $T_{1/2}$ in rodents, cyno, and dog sufficient for oral daily dosing
PD Model	✓ Iron reduction after single and repeat oral dosing to dog and monkey to support once-daily oral dosing ✓ Sustained iron reduction for 16 hr
Efficacy Model	✓ Efficacy in the erythropoietin (EPO)-induced mouse model for erythrocytosis ✓ Reduction of hemoglobin and hematocrit after repeat oral dosing to cynos
DDI	✓ No DDI risk potential
Safety	✓ No major off-target activities ✓ Tolerated in 7-day rat MTD

Phase 1 initiation by year-end
PK/PD based preliminary clinical PoC achievable in phase 1

Protagonist Therapeutics

PN-8047: Oral Hepcidin Functional Mimetic Development Timelines



Protagonist Therapeutics

Protagonist Therapeutics

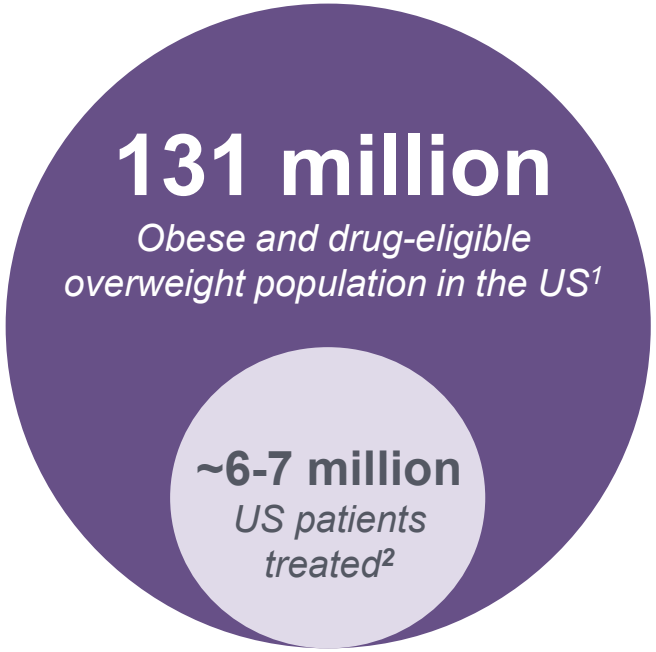
Anti-Obesity Therapeutics: Dominated by injectable appetite-suppressing hormone peptide mimetics

Oral Peptide agents offer a strong differentiation and address unmet medical need

Obesity: Unprecedented Pharmaceutical Opportunity in the US and Worldwide

Only ~5% of Eligible Patients Receive Drug Treatment[1]

Massive Untapped Opportunity in Obesity Care



- Obesity is a global epidemic
  - In 2024, nearly ***40% of Americans were obese*** or considered drug-eligible overweight[3]
- Low Treatment Penetration
  - Only ~5% of eligible patients receive drug treatment[1]
- Current challenges with anti-obesity drugs
  - Convenience; needle avoidance
  - Early days & limited options
  - Adverse effects

‘Oral’ and ‘more effective’ agents:
An attractive option for a chronic condition and affiliated co-morbidities

Protagonist Therapeutics

[1] Clarivate Disease Landscape & Forecast – Obesity/Overweight (November 2025); Drug-eligible Population: obese (BMI≥30) and drug-eligible overweight (27≤BMI<30 with at least one weight-related comorbidity); [2]Morgan Stanley Research, May 2026; Bernstein Research, May 2026; [3]HSBC Research, Dec 2025.

Desirable Features for Next Generation Anti-Obesity Candidate

- Currently approved therapies:
  - Semaglutide (Wegovy® *Injectable*): Mono GLP-1R agonist – 13.7% body weight loss[1]
  - Semaglutide (Wegovy® *Pill*): Mono GLP-1R agonist – 13.6% body weight loss[2]
  - Tirzepatide (Zepbound®): Dual GLP-1R and GIPR agonist – 20.2% body weight loss[1]
  - Orforglipron (Foundayo™ *Pill*): GLP-1R agonist – 11.1% body weight loss (without diabetes)[3]; 9.6% body weight loss (with type 2 diabetes)[4]
- Retatrutide (injectable; triple agonist) in Ph3 development[5]

Proprietary Peptide Technology

An ORAL Triple-Agonist Peptide (GLP-1R/GIPR/GCGR)

- Potential improvements
  - **Oral option**
  - Magnitude of body weight loss
    - Potential secondary benefits in co-morbidities (diabetes, CVD, OSA, CKD, MASH etc.)
  - Improving tolerability: mainly GI (nausea, vomiting)
  - Favorable fat vs. lean mass loss

Protagonist Therapeutics

1. Aronne LJ, et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. *N Engl J Med*. 2025;393:26-36; 2. Wharton S, et al. OASIS 4 Study Group. Oral semaglutide at a dose of 25 mg in adults with overweight or obesity. *N Engl J Med* 2025;393:1077-87; 3. Wharton S, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment. *N Engl J Med* 2025;393:1796-806; 4. Horn DB, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, for the treatment of obesity in people with type 2 diabetes (ATTAIN-2): a phase 3, double-blind, randomised, multicentre, placebo-controlled trial. *Lancet*. 2026;406(10522):2927-44; 5. Jastreboff AM, et al. Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. *N Engl J Med* 2023;389:514-26.

PN-477: A Novel Triple GLP/GIP/GCG Receptors Agonist Peptide

Optionality for Oral or Subcutaneous Dosing

Potential Improvements

- **Magnitude** and **quality** of body weight loss
  - Potential secondary benefits in co-morbidities (diabetes, CVD, OSA, CKD, MASH etc.)
  - Favorable fat vs. lean mass loss
- Improving **tolerability**: mainly GI (nausea, vomiting)
- Maximize **optionality** of one drug substance with two formulations (oral or sc injectable)

ORAL Triple-Agonist Once-daily Dosing → **PN-477o**

Injectable Triple-Agonist Once-weekly Dosing → **PN-477sc**

GLP-1R: Glucagon-Like Peptide-1 Receptor
GIPR: Gastric Inhibitory Polypeptide Receptor
GCGR: Glucagon Receptor

Protagonist Therapeutics

PN-477 Oral Triple Agonist (GLP-1R, GIPR, GCGR) Peptide

Novel Chemical Entity, Oral Triple Agonist, Potent, and Stable in GI Fluids

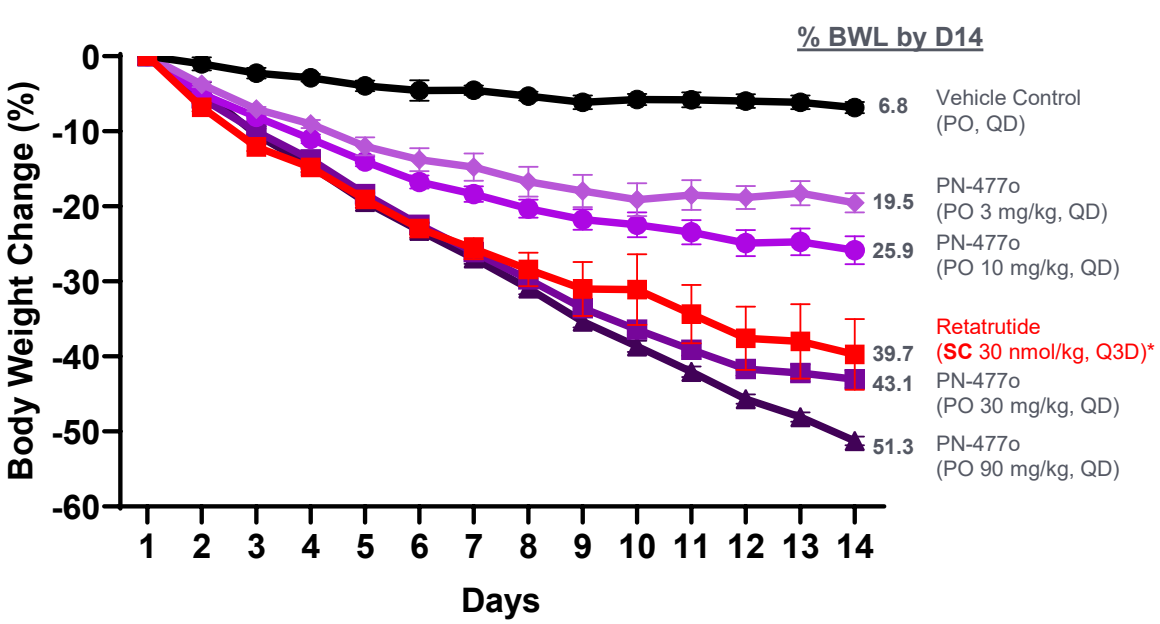
Attribute	Criteria
Potency	✓ nM potency vs GLP-1R, GIPR, GCGR
Stability	✓ Stable in simulated gastric and intestinal fluids ✓ Stable in serum ✓ Metabolic stability ✓ Thermostability
Efficacy Model	✓ Mouse Diet Induced Obesity (DIO) model
in vivo Pharmacodynamics	✓ Glucose control with glucose tolerance test
in vivo Pharmacokinetics	✓ Oral bioavailability demonstrated in mouse, rat, dog, cynomolgus monkey ✓ GI stability and Oral PK supports once-a-day oral dosing ✓ PK profile supports once-a-week subcutaneous dosing

GI: Gastrointestinal; PK: Pharmacokinetic

Oral PN-477o and Subcutaneous PN-477sc

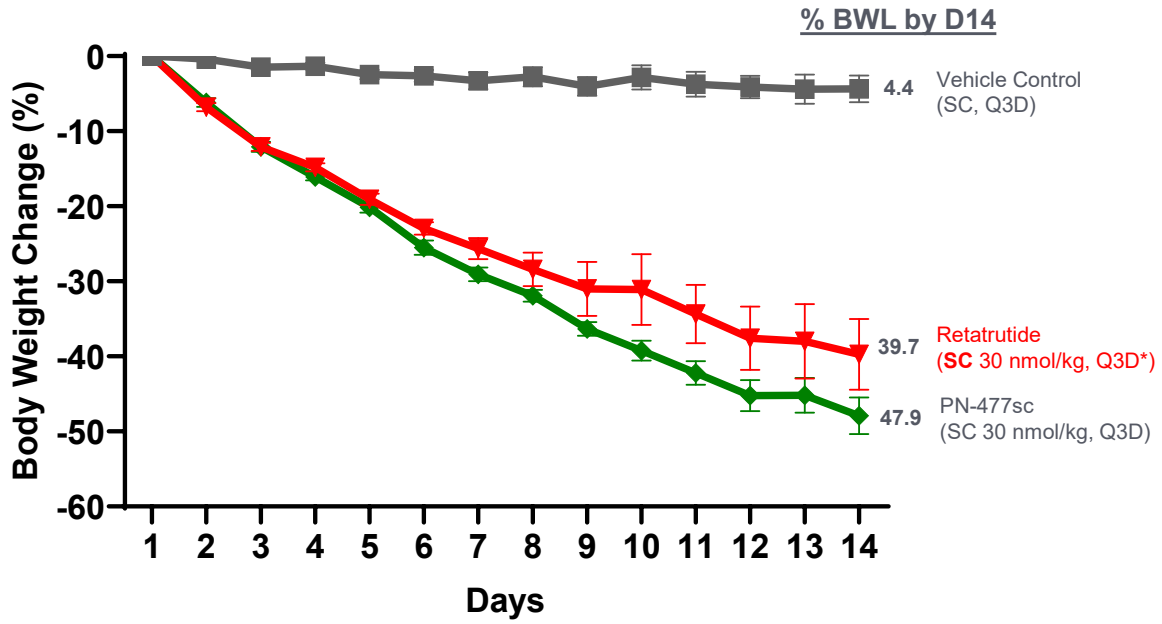
DIO Mice Study #1

% Body Weight Change, PO: Days 1-14



- Dose Proportional Body Weight Loss of Up to 50% with Oral PN-477o

% Body Weight Change, SC: Days 1-14



- Subcutaneous PN-477sc Achieves Body Weight Loss Comparable to Retatrutide

Protagonist Therapeutics

BWL: Body Weight Loss; DIO: Diet Induced Obese; Data points depict mean ± SEM. PO = per os (oral), SC = subcutaneous, QD = once a day, Q3D = every 3 days.
* Retatrutide SC 30 nmol/kg dose is the highest dose reported for DIO mouse efficacy study (Cell Metabolism 34, 1234–1247, September 6, 2022).

PN-477: A Potential Best-in-Class Triple Agonist Anti-Obesity Peptide With Convenience of Once-Daily Oral and Once-Weekly SC Dosing

- Novel, orally stable, and potent triple agonist (GLP-1R, GIPR, and GCGR)
- Engineered balance of GLP-1R, GIPR, GCGR absolute and relative potencies
  - Designed to provide maximal weight loss and optimal body composition of retatrutide and GI tolerability of tirzepatide
- Weight loss in DIO mice benchmarks favorably versus retatrutide
  - Dose-proportional body weight loss of up to 50% in DIO mouse model achieved with oral administration of PN-477o
  - PN-477sc provides similar body weight loss as retatrutide with equivalent SC dose
  - Preferential fat mass to lean mass loss observed; similar to retatrutide
- Weight loss after single dose of PN-477sc benchmarks favorably versus retatrutide in normal dogs and monkeys
- PK profiles after Oral and SC dosing in normal dogs and monkeys support:
  - **PN-477o**: Once-daily ORAL Triple-Agonist Peptide
  - **PN-477sc**: Once-weekly injectable Triple-Agonist Peptide
- IND-enabling studies underway

PN-477: Near-Term Clinical Development Plan

PN-477sc* Anti-Obesity

1H 2026	2H 2026	1H 2027	2H 2027
❖ PN-477sc Ph1 initiation (mid-2026)	❖ PN-477sc Ph1 SAD; Clinical PoC**	❖ PN-477sc Ph1 SAD topline ❖ PN-477sc Ph1 MAD initiation	❖ PN-477sc Ph1 MAD topline

PN-477o* Anti-Obesity

1H 2026	2H 2026	1H 2027	2H 2027
		❖ PN-477o Ph1 initiation (Q1'27)	❖ PN-477o Ph1 SAD Topline

*PN-477sc weekly sc dosing; PN-477o once daily oral dosing

**Phase 1 study results could provide preliminary clinical PoC

Protagonist Therapeutics

PN-458: A Highly Potent Oral Dual GLP-1/GIP Receptor Agonist

Potential Weight Loss Profile and GI Tolerability of Tirzepatide

	Human EC_{50} (nM)		
	GLP-1R	**GIPR**	**GCGR**
Retatrutide[2,‡] (Eli Lilly **Triple** GLP-1R/GIPR/GCGR)	14.6	1.6	19.2
PN-477	6.4	0.4	14.8
Tirzepatide[1,‡] (Eli Lilly **Dual** GLP-1R/GIPR)	23.1	1.7	NA†
PN-458	**7.8**	**0.86**	**NA†**

‡Sourced from *1PlusChem Cat.1P01MVTY (Tirzepatide); MCE Cat. HY-P3506 (Retatrutide)*

† ***NA: Not Active***

- PN-458 has higher potency than tirzepatide for GLP-1R and GIPR
- Higher GIPR potency may be favorable for better GI tolerability[3,4]

Protagonist Therapeutics

[1]Coskun T, Mol Metab 2018; [2]Coskun T, Cell Metab 2022; [3]Campbell JE, Cell Metabolism 2023; [4]El K, Sci Adv 2021

PN-458 Dual Agonist (GLP-1R, GIPR) Peptide

Novel Chemical Entity, Oral Dual Agonist, Potent, and Stable in GI Fluids

Attribute	Criteria
Potency	✓ nM potency vs GLP-1R, GIPR
Stability	✓ Stable in simulated gastric and intestinal fluids ✓ Stable in serum ✓ Metabolic stability ✓ Thermostability
Efficacy Model	✓ Mouse Diet Induced Obesity (DIO) model
in vivo Pharmacodynamics	✓ Glucose control with glucose tolerance test
in vivo Pharmacokinetics	✓ Oral bioavailability demonstrated in mouse, rat, dog, cynomolgus monkey ✓ GI stability supports once-a-day oral dosing ✓ Plasma PK profile supports once-a-week subcutaneous dosing

GI: Gastrointestinal; PK: Pharmacokinetic

IND-enabling studies in progress

Protagonist Therapeutics

PN-458: A Potential Best-in-Class Dual Agonist Anti-Obesity Peptide Development Candidate with Convenience of Once-Daily Oral and Once-Weekly SC Dosing

- Novel, orally stable, and potent dual agonist (GLP-1R and GIPR)
- Engineered balance of GLP-1R and GIPR absolute and relative potencies
- Weight loss in DIO mice benchmarks favorably versus tirzepatide
- Weight loss after single dose of PN-458o and sc benchmarks favorably versus tirzepatide in normal monkeys
- PK profiles in dogs and monkeys support once-daily (PN-458o) and once weekly dosing (PN-458sc)
- IND-enabling studies underway

Building a Portfolio of ORAL and Injectable Anti-Obesity Agents

PN-458: A Dual GLP-1R/GIPR Oral & SC Agonist

- **Tirzepatide** (Zepbound®): The only approved dual GLP-1R/GIPR therapy
  - Best-in-class: Body weight loss ~20.2%[1]
  - Best-selling anti-obesity drug
  - **Injectable**
- **PN-458**: Dual GLP-1R/GIPR agonist
  - Optionality: **Oral** and SC
  - Pre-clinical PoC
  - Ph1 initiation Q4 '26
- **Amylin**:
  - Mono- and poly-agonists
  - Oral and SC

ORAL Dual-Agonist
Once-daily Dosing

PN-458o

Injectable Dual-Agonist
Once-weekly Dosing

PN-458sc

Protagonist Therapeutics

1. Aronne LJ, et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. N Engl J Med. 2025;393(1):26-36.

Protagonist Therapeutics

What's Next?

Protagonist Therapeutics

Expected Clinical Trial Initiations, Data Readouts, and Development Candidate Nominations

	1H 2026	2H 2026	2027
ICOTYDE Partner: J&J	❖ Psoriasis NDA & MAA ❖ Ph3 PsA 1 & 2; UC & CD ongoing	★ **ICOTYDE approved for Plaque Psoriasis** ❖ **Ph3 ICONIC-ASCEND and PsA 1 Primary Completion**	❖ Commercial	❖ Commercial ❖ **Ph3 ICONIC-PsA 2 Primary Completion**
Rusfertide Partner: Takeda	❖ NDA submitted	❖ NDA accepted; priority review granted ❖ Opted-out	★ **Potential US approval/launch for PV**	❖ Commercial
PN-881*	Oral IL-17 antagonist ❖ Ph1 ongoing	❖ Ph1 ongoing	❖ **Ph1 completion: PK** ❖ Ph2 PsO Initiation	❖ Potential Phase 2 Initiation (eg, PsA, HS)
PN-477sc* **PN-477o***	Anti-obesity DCs ❖ IND-enabling studies	❖ PN-477sc Ph1 initiation (mid-2026)	❖ **PN-477sc Ph1 SAD; Clinical PoC**	❖ **PN-477sc Ph1 SAD Topline, MAD Initiation, MAD PoC** ❖ **PN-477o Ph1 initiation (Q1'27) and SAD Topline**
PN-8047*	❖ Oral Hepcidin DC	❖ IND-enabling studies	❖ IND-enabling studies ❖ Ph1 initiation	❖ **Ph1 Clinical PoC**
PN-458sc* **PN-458o***	Dual GLP/GIP DCs ❖ PN-458sc ❖ PN-458o		❖ Ph1 initiation	❖ **Ph1 Clinical PoC**
Discovery*	❖ AmylinR-based mono & poly-agonists ❖ Oral IL-4Rα antagonist			

*Fully owned by Protagonist Therapeutics, Inc.
DC, Development candidate; ready for IND-enabling studies.

Protagonist Therapeutics

Thank you

Protagonist Therapeutics

Appendix

List of key peer-reviewed manuscripts, posters, and oral presentations

ICOTYDE™ (Icotrokinra; JNJ-77242113; PN-235)

Congresses: Key Posters and Oral Presentations

For posters and presentations relating to ICOTYDE™, please double-click on the icon to the left (link and site maintained by Johnson & Johnson)

ICOTYDE™ (Icotrokinra; JNJ-77242113; PN-235)

Peer-Reviewed Manuscripts (double click on icon to open manuscript)

- Double-click on icon to open manuscript

Strawn D, et al. Icotrokinra induces early and sustained pharmacodynamic responses in phase IIb study of patients with moderate-to-severe psoriasis. *JCI Insight*. 2025;10(24):e193563.

Gooderham M, et al. Targeted Oral Peptide Icotrokinra for Psoriasis Involving High-Impact Sites. *NEJM Evid*. 2025;4(12):EVIDoa2500155.

Bissonnette R, et al. Oral Icotrokinra for Plaque Psoriasis in Adults and Adolescents. *N Engl J Med*. 2025;393(18):1784-95.

Gold LS, et al. Once-daily oral icotrokinra versus placebo and once-daily oral deucravacitinib in participants with moderate-to-severe plaque psoriasis (ICONIC-ADVANCE 1 & 2): two phase 3, randomised, placebo-controlled and active-comparator-controlled trials. *Lancet*. 2025;406(10510):1363-74.

ICOTYDE™ (Icotrokinra; JNJ-77242113; PN-235)

Peer-Reviewed Manuscripts (continued; double click on icon to open manuscript)

- Double-click on icon to open manuscript

Knight B, et al. Translational Pharmacokinetics of Icotrokinra, a Targeted Oral Peptide that Selectively Blocks Interleukin-23 Receptor and Inhibits Signaling. *Dermatol Ther (Heidelb)*. 2025;15(9):2495-520.

Stein Gold L, et al. Oral Peptide Therapeutics as an Emerging Treatment Modality in Immune-Mediated Inflammatory Diseases: A Narrative Review. *Adv Ther*. 2025;42(7):3158-72.

Ferris LK, et al. FRONTIER-2: A phase 2b, long-term extension, dose-ranging study of oral JNJ-77242113 for the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2025;92(3):495-502.

Fourie AM, et al. JNJ-77242113, a highly potent, selective peptide targeting the IL-23 receptor, provides robust IL-23 pathway inhibition upon oral dosing in rats and humans. *Sci Rep*. 2024;14(1):17515.

Bissonnette R, et al. An Oral Interleukin-23-Receptor Antagonist Peptide for Plaque Psoriasis. *N Engl J Med*. 2024;390(6):510-21.

Rusfertide (PTG-300)

Peer-Reviewed Manuscripts (double click on icon to open manuscript)

- Double-click on icon to open manuscript

Chew LP, et al. Rusfertide rapidly decreases hematocrit in patients with suboptimally controlled polycythemia vera. *Leuk Res*. 2025;159:108132.

Modi NB, et al. Evaluation of Rusfertide, a Hepcidin Mimetic, on Cardiac Repolarization: A Randomized, Placebo- and Positive-Controlled Crossover Thorough QT Study in Healthy Participants. *Clin Ther*. 2025;47(11):1043-52.

Modi NB, et al. Multiple-Dose Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Subcutaneous Rusfertide, a Hepcidin Mimetic, in Healthy Subjects. *Clin Pharmacol Drug Dev*. 2025;14(4):311-23.

Modi NB, et al. Pharmacokinetics and Pharmacodynamics of Rusfertide, a Hepcidin Mimetic, Following Subcutaneous Administration of a Lyophilized Powder Formulation in Healthy Volunteers. *Drugs R D*. 2024;24(4):539-52.

Rusfertide (PTG-300)

Peer-Reviewed Manuscripts (continued; double click on icon to open manuscript)

- Double-click on icon to open manuscript

Modi NB, et al. Pharmacokinetics, pharmacodynamics, and tolerability of an aqueous formulation of rusfertide (PTG-300), a hepcidin mimetic, in healthy volunteers: A double-blind first-in-human study. *Eur J Haematol*. 2024;113(3):340-50.

Kuykendall AT, et al. Contemporary Challenges in Polycythemia Vera Management From the Perspective of Patients and Physicians. *Clin Lymphoma Myeloma Leuk*. 2024;24(8):512-22.

Kremyanskaya M, et al. Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera. *N Engl J Med*. 2024;390(8):723-35.

Kowdley KV, et al. Rusfertide for the treatment of iron overload in HFE-related haemochromatosis: an open-label, multicentre, proof-of-concept phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8(12):1118-28.

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2025 (double-click on icon to open presentation)

- **67th American Society of Hematology (ASH) Annual Meeting and Exposition**
  - 6-9 December 2025; Orlando, FL

    Kuykendall AT, et al. Rusfertide or placebo plus current standard-of-care therapy for polycythemia vera: Durability of response and safety results through week 52 from the randomized controlled phase 3 VERIFY study.

    Bankar A, et al. Comprehensive Analyses of Patient-Reported Outcomes from the Phase 3 VERIFY Study of Rusfertide or Placebo Plus Current Standard of Care for Polycythemia Vera.

    Shatzel J, et al. Should Dermatologic Examinations Become Routine Standard of Care in Patients with Polycythemia Vera, Observations from the Phase 3 VERIFY Study Prior to Rusfertide Exposure.

- **Society of Hematologic Oncology (SOHO) Annual Meeting**
  - 3-6 September 2025; Houston, TX

    Pemmaraju N, et al. Results from VERIFY, An International, Randomized Phase 3 Double-blind Placebo-controlled Study of Rusfertide (First-In-Class Hepcidin Mimetic) for Treatment of Polycythemia Vera (PV).

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2025 (continued; double-click on icon to open presentation)

- **MPN Workshop of the Carolinas**
  - 22-23 August 2025; Charlotte, NC

Pemmaraju N, et al. VERIFY, A Phase 3 Placebo-Controlled Study Investigating Rusfertide With Current Standard of Care Therapy in Patients With Polycythemia Vera.

- **American Society of Clinical Oncology Annual Meeting**
  - 30 May-3 June 2025; Chicago, IL

Kuykendall et al. Results from VERIFY, a phase 3, double-blind, placebo (PBO)-controlled study of rusfertide for treatment of polycythemia vera (PV).

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2024 (double-click on icon to open presentation)

- **66th American Society of Hematology (ASH) Annual Meeting and Exposition**
  - 7-10 December 2024; San Diego, CA

Gerds A, et al. Final Results from the Phase 2 REVIVE Study Investigating the Hepcidin Mimetic Rusfertide in Patients with Polycythemia Vera (PV).

- **16th International Congress on Myeloproliferative Neoplasms (MPN Congress)**
  - 24-25 October 2024; Brooklyn, NY

Gerds A, et al. Updated Long-Term Results from the Phase 2 REVIVE Study Investigating the Hepcidin Mimetic Rusfertide in Polycythemia Vera Patients: Hematocrit Control and Therapeutic Phlebotomy Frequency.

- **American College of Clinical Pharmacology (ACCP) Annual Meeting**
  - 8-10 September 2024; N. Bethesda, MD

Modi N, et al. Pharmacokinetics, Pharmacodynamics and Safety of Rusfertide, a Hepcidin Mimetic, in Subjects with Hepatic Impairment and in Subjects with Renal Impairment.

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2024 (continued; double-click on icon to open presentation)

- **European Hematology Association (EHA) Meeting**
  - 13-16 June 2024; Madrid, Spain

Pettit KM, et al. Updated Long-Term Results from the Phase 2 REVIVE Study Investigating the Hepcidin Mimetic Rusfertide in Polycythemia Vera Patients: Hematocrit Control and Therapeutic Phlebotomy Frequency

- **American Society of Clinical Oncology (ASCO) Annual Meeting**
  - 31 May-4 June 2024; Chicago, IL

Bankar A, et al. VERIFY: A Randomized Controlled Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera (PV)

- **10th Translational Research Conference: Myeloproliferative Neoplasms**
  - 26-28 April 2024; Mandelieu-La Napoule, France

Modi N, et al. Biomarker Profiling of Patients with Polycythemia Vera Relative to Healthy Subjects: Baseline Characteristics of Patients Enrolled in the PACIFIC Study

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2023 (double-click on icon to open presentation)

- **65th American Society of Hematology (ASH) Annual Meeting and Exposition**
  - 9-12 December 2023; San Diego, CA


Ritchie EK, et al. Durability of Hematocrit Control in Polycythemia Vera With the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results From the REVIVE Study.


Kuykendall AT, et al. Real-World Analysis of Thromboembolic Event Rates in Patients in the United States with Polycythemia Vera.


Ginzburg Y, et al. Rusfertide Improves Markers of Iron Deficiency in Patients With Polycythemia Vera.


Pemmaraju N, et al. Prevalence Of Second Cancers In Patients With Polycythemia Vera (PV): A Retrospective Analysis Of US Real-World Claims Data.

- **15th International Congress on Myeloproliferative Neoplasms (MPN Congress)**
  - 2-3 November 2023; Brooklyn, NY


Pemmaraju N, et al. Summary of Malignancies Observed Across 5 Phase 2 Open Label Clinical Trials of the Hepcidin Mimetic Rusfertide.

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2023 (continued; double-click on icon to open presentation)

- **Society of Hematologic Oncology (SOHO) Annual Meeting**
  - 6-9 September 2023; Houston, TX

Pemmaraju N, et al. Targeted Therapy of Uncontrolled Erythrocytosis in Polycythemia Vera with the Hepcidin Mimetic, Rusfertide: Blinded Randomizated Withdrawal Results of the Phase 2 REVIVE Study.

- **European Hematology Association (EHA) Meeting**
  - 8-11 June 2023; Frankfurt, Germany

Kremyanskaya M, et al. Targeted Therapy Of Uncontrolled Erythrocytosis In Polycythemia Vera With The Hepcidin Mimetic, Rusfertide: Blinded Randomized Withdrawal Results Of The REVIVE Study.

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2022 (double-click on icon to open presentation)

- **64th American Society of Hematology (ASH) Annual Meeting and Exposition**
  - 10-13 December 2022; New Orleans, LA


Pemmaraju N, et al. Analysis Of Adverse Events Following Rusfertide Dosing In REVIVE: A Phase 2 Study In Patients With Polycythemia Vera.


Pemmaraju N, et al. Subgroup Analysis Of Adverse Events Following Rusfertide Dosing In REVIVE: A Phase 2 Study In Patients With Polycythemia Vera.


Verstovsek S, et al. VERIFY: A Phase 3 Study Of The Hepcidin Mimetic Rusfertide (PTG-300) In Patients With Polycythemia Vera.

- **Society of Hematologic Oncology (SOHO) Annual Meeting**
  - 28 September-1 October 2022; Houston, TX


Pemmaraju N, et al. Rusfertide (PTG-300) Treatment Interruption Reverses Hematological Gains and Upon Reinitiation, Restoration of Clinical Benefit is Observed in Patients With Polycythemia Vera.

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2022 (continued; double-click on icon to open presentation)

- **European Hematology Association (EHA) Meeting**
  - 9-17 June 2022; Vienna, Austria

Kuykendall A, et al. PTG-300 (Rusfertide) Treatment Interruption Reverses Hematological Gains And Restores Therapeutic Benefit On Reinitiation In Subjects With Polycythemia Vera.

- **American Society of Clinical Oncology (ASCO) Annual Meeting**
  - 3-7 June 2022; Chicago, IL

Hoffman R, et al. Rusfertide (PTG-300) Treatment in Phlebotomy-Dependent Polycythemia Vera.

Rusfertide (PTG-300)

Key Poster and Oral Presentations—2021 (double-click on icon to open presentation)

- **63rd American Society of Hematology (ASH) Annual Meeting and Exposition**
  - 11-14 December 2021; Atlanta, Georgia


Hoffman R, et al. Rusfertide (PTG-300) Controls Hematocrit Levels and Essentially Eliminates Phlebotomy Requirement in Polycythemia Vera Patients.


Ginzburg Y, et al. Rusfertide (PTG-300) Induction Therapy Rapidly Achieves Hematocrit Control in Polycythemia Vera Patients without the Need for Therapeutic Phlebotomy.


Verstovsek S, et al. A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera.


Kowdley K, et al. Rusfertide (PTG-300), A Hepcidin Mimetic, Maintains Liver Iron Concentration in the Absence of Phlebotomies in Patients with Hereditary Hemochromatosis.


Taranath R, et al. Regulation of Iron Homeostasis and Efficacy of Rusfertide Analog Peptide in a Mouse Model for Polycythemia Vera.

PN-881 (Oral IL-17 Antagonist)

Key Oral Presentations—2025 (double-click on icon to open presentation)

- **European Academy of Dermatology and Venerology (EADV) Congress**
  - 17-20 September 2025; Paris, France

Manrique M, et al. PN-881: First-in-class oral peptide targeting the IL-17 pathway.

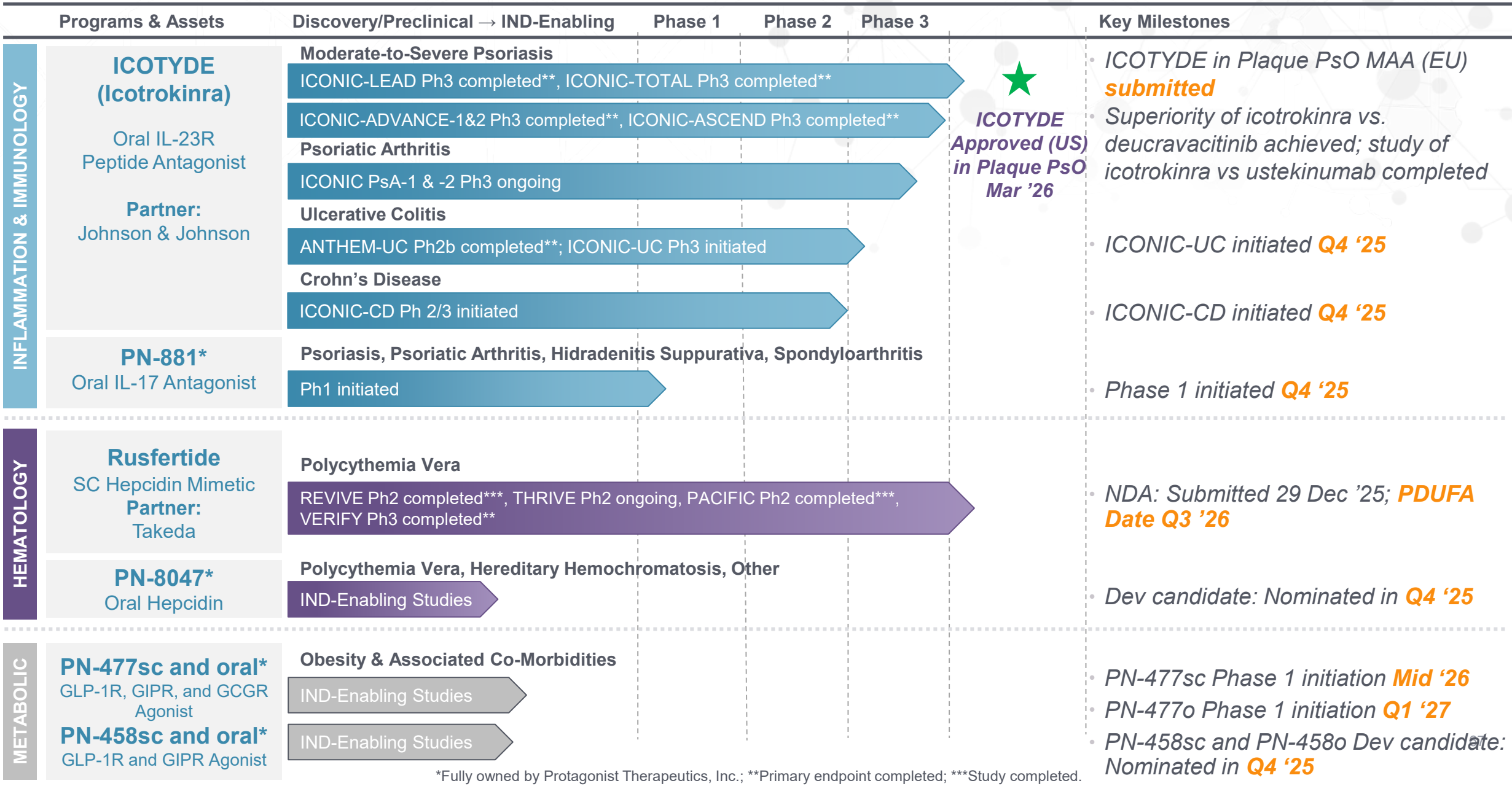
- **Society For Investigative Dermatology (SID) Congress**
  - 7-10 May 2025; San Diego, CA

Manrique M, et al. PN-881: First-in-class oral peptide targeting the IL–17 pathway.

Protagonist Therapeutics

Back up Slides

Pipeline of Proprietary and Partnered Drug Candidates



*Fully owned by Protagonist Therapeutics, Inc.; **Primary endpoint completed; ***Study completed.

Icotrokinra Clinical Development Program

Successful Studies in Psoriasis & UC; PsA studies Ongoing; Phase 3 UC and CD studies underway

	Reference(s) or Primary Completion Dates	Primary Endpoint Met?
Plaque Psoriasis		
FRONTIER 1[1] & 2[2] Ph2b, n = 255 & 227, in moderate-to-severe psoriasis	Bissonnette R, et al. *N Engl J Med.* 2024;390:510-21.	✓
ICONIC-LEAD[3] Ph3, n = 684, in moderate-to-severe psoriasis	Bissonnette R, et al. *N Engl J Med.* 2025;393:1784-95.	✓
ICONIC-TOTAL[4] Ph3, n = 311, psoriasis in special areas of body	Gooderham M, et al. *NEJM Evid.* 2025;Epub ahead of print.	✓
ICONIC-ADVANCE 1[5] Ph3, n = 774, Icotrokinra vs. Deucravacitinib	Gold LS, et al. *Lancet.* 2025;406:1363-74.	✓
ICONIC-ADVANCE 2[6] Ph3, n = 731, Icotrokinra vs. Deucravacitinib		✓
Pustular/Erythrodermic Psoriasis[7] Ph3, n = 19		✓
ICONIC-ASCEND[8] Ph3, n = 752, Icotrokinra vs. Ustekinumab	**Nov '25**	
Psoriatic Arthritis		
ICONIC-PsA 1[9] Ph3, n ~ 540, in biologic-naive active psoriatic arthritis	**~May '26**	
ICONIC-PsA 2[10] Ph3, n ~ 750, in biologic exposed active psoriatic arthritis	**~Feb '27**	
Ulcerative Colitis		
ANTHEM-UC[11] Ph2b, n = 252, in ulcerative colitis		✓
ICONIC-UC[12] Ph3, n ~ 882, in ulcerative colitis	**~Jan '28**	
Crohn's Disease		
ICONIC-CD[13] Ph 2/3, n ~ 1092, in Crohn's disease	**~Sept '28**	

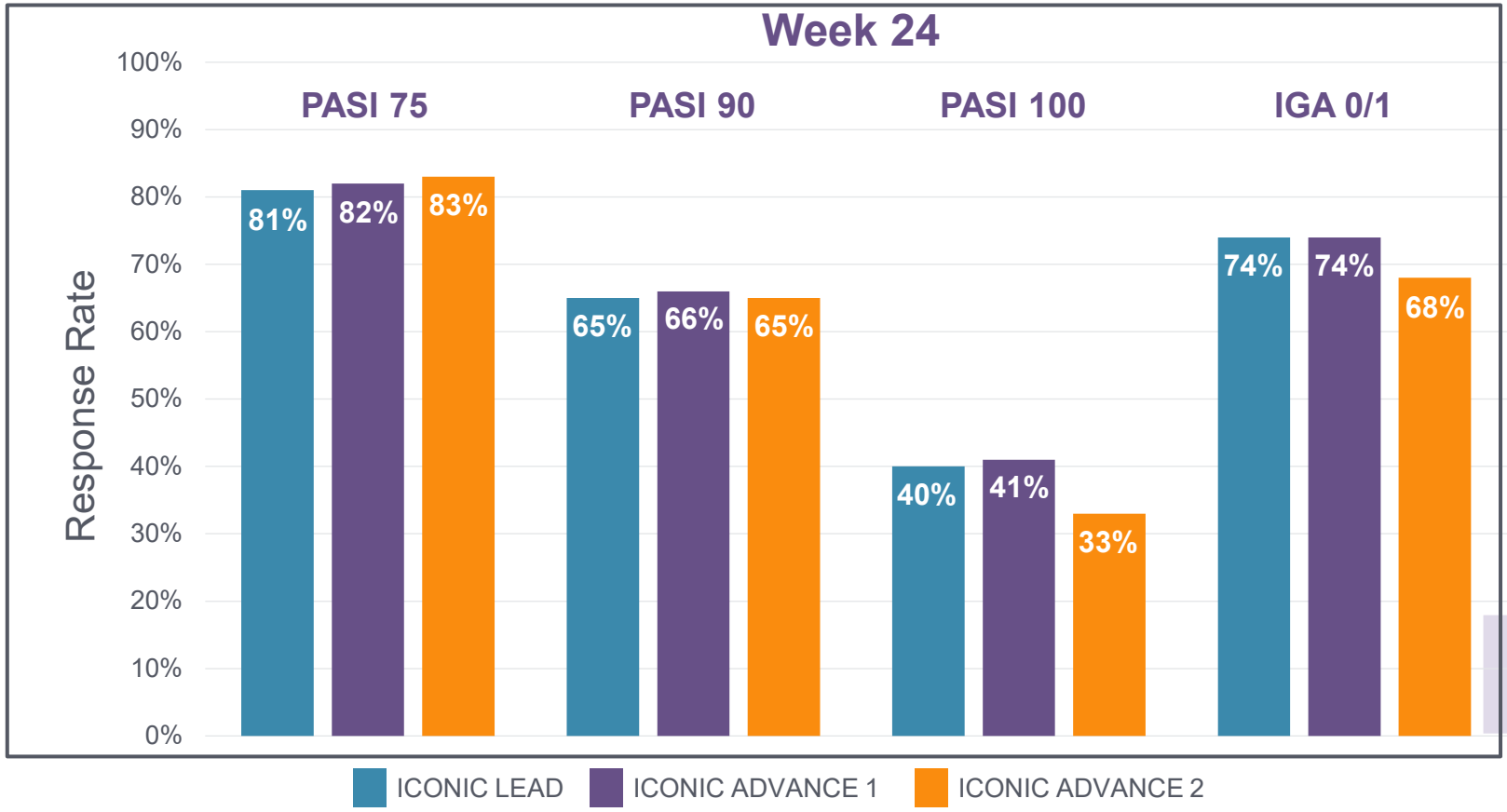
Protagonist Therapeutics

1. FRONTIER 1: NCT05223868
2. FRONTIER 2: NCT05364554
3. ICONIC-LEAD: NCT06095115
4. ICONIC-TOTAL: NCT06095102
5. ICONIC-ADVANCE 1: NCT06143878
6. ICONIC-ADVANCE 2: NCT06220604
7. Japan Ph3: NCT06295692
8. ICONIC-ASCEND: NCT06934226
9. ICONIC-PsA 1: NCT06878404
10. ICONIC-PsA 2: NCT06807424
11. ANTHEM-UC: NCT06049017
12. ICONIC-UC: NCT07196748
13. ICONIC-CD: NCT07196722

Icotrokinra: Established Safety with Best-in-Class Oral Efficacy

ICONIC LEAD and ADVANCE Phase 3 Trial Results

Efficacy:
High rates of skin clearance with early onset and durable response



Safety:
Icotrokinra broadly comparable to placebo

- AE-related ***discontinuations similar to or lower than placebo***
- AE and SAE rates ***comparable to placebo***
- Infection rates, including viral, generally comparable
- Common AEs (e.g., headache, GI) not meaningfully different

Sustained 67% IGA 0/1 response to Week 52

NDA filed for plaque psoriasis: July '25

Protagonist Therapeutics

ICONIC LEAD NEJM Nov 2025; ICONIC ADVANCE 1&2 Lancet Sep 2025
PASI, Psoriasis Area and Severity Index. IGA, Investigator's Global Assessment;

Phase 3 ICONIC LEAD Study: Icotrokinra in Moderate-to-Severe PsO in Adults and Adolescents (N=684)[1,2]

Week 16 Efficacy Summary: Co-Primary and Key Secondary Endpoints

- In the pivotal ICONIC-LEAD study, icotrokinra demonstrated significantly higher rates of clear/almost clear skin and scalp disease and PsO symptom relief in adults and adolescents vs. placebo at Week 16
- Icotrokinra showed separation from placebo as early as Week 8

	Week 16: Adults (≥18 years old) and Adolescents (≥12 years to <18 years old)[1]							
ICONIC-LEAD	**IGA 0/1***	**PASI 90***	**PASI 75**	**IGA 0**	**PASI 100**	**PSSD Itch**	**PSSD Symptom 0**	**ss-IGA 0/1**
Placebo	8	4	11	1	<1	13	1	15
Icotrokinra 200 mg QD	65 **(Δ+56.4)**	50 **(Δ+45.1)**	69 **(Δ+58)**	33 **(Δ+32)**	27 **(Δ+26)**	58 **(Δ+45)**	20 **(Δ+19)**	72 **(Δ+57)**

*Co-primary endpoints. IGA, Investigator's Global Assessment; IGA 0/1, IGA score 0/1 & ≥2-grade improvement from baseline.
NA, not available; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; QD, once-daily.
All values represent percentages unless stated otherwise. **Orange** numbers in parentheses show the difference between icotrokinra and placebo for each stated endpoint.

Protagonist Therapeutics

1. Presented at the 12th Annual Meeting of International Dermatology Outcomes Measures (IDEOM); Washington, D.C., USA; June 27–28, 2025.

Phase 3 ICONIC LEAD Study[1]

ICO AE Profile Through Week 52 Was Consistent With That Observed Through Week 16

	PBO-Controlled (Adults & Adolescents)		Active Treatment (Adults & Adolescents)		ICO Responders Re-Randomized at Week 24 (Adults)	
AEs Through Week 52	ICO (Week 0-16; N=456)	PBO (Week 0-16; N=228)	ICO (Week 16-52; N=213)[a]	ICO (Week 0-52; N=456)	ICO → ICO (Week 24-52; N=168)	ICO→PBO (Week 24-52; N=172)[b]
Mean weeks of follow-up	15.9	15.8	35.3	43.4	27.7	27.8
Any AE	226 (50%)	112 (49%)	132 (62%)	313 (69%)	92 (55%)	82 (48%)
Most Common AEs						
Nasopharyngitis	31 (7%)	15 (7%)	23 (11%)	64 (14%)	21 (12%)	20 (12%)
Upper respiratory tract infection	30 (7%)	16 (7%)	24 (11%)	52 (11%)	9 (5%)	15 (9%)
SAE (Serious Adverse Event)	6 (1%)	6 (3%)	4 (2%)	16 (4%)	3 (2%)	5 (3%)
Serious infection	1 (<1%)	0	1 (<1%)	1 (<1%)	0	1 (1%)
AE Leading to Discontinuation	6 (1%)	1 (<1%)	4 (2%)	10 (2%)	1 (1%)	3 (2%)
Gastrointestinal AE[c]	26 (6%)	13 (6%)	9 (4%)	51 (11%)	7 (4%)	8 (5%)
Active TB	0	0	0	0	0	0
Malignancy[d]	2 (<1%)	0	0	2 (<1%)	0	0

Safety analysis set included all randomized and treated participants. [a]Includes data after Week 16 for PBO-randomized participants who crossed over to receive ICO. [b]Combined withdrawal and retreatment group. [c]Based on gastrointestinal disorders SOC. [d]Included adenocarcinoma of colon and prostate cancer. AE, adverse event; ICO, icotrokinra; PBO, placebo; SAE, serious adverse event; SOC, system organ class; TB, tuberculosis.

Protagonist Therapeutics

1. Presented at the 2025 SDPA 23rd Annual Fall Dermatology Conference; November 5-9, 2025; San Antonio, TX, USA.

Phase 3 ICONIC-TOTAL Study: Plaque PsO and Difficult-to-Treat High Impact Sites (N=311)[1-3]

Week 16 Efficacy Summary: Co-Primary and Key Secondary Endpoints

- Icotrokinra demonstrated significantly higher rates of clear/almost clear skin in difficult-to-treat areas, including the scalp and genital areas, hand and foot, and nail psoriasis vs. placebo
- ICO-treated patients achieved significantly higher response rates, including meaningful improvements in the scalp and genital areas, vs placebo at Week 16

	Week 16										
			Scalp				Genital				Hand/ Foot:
ICONIC-TOTAL	IGA 0/1*	IGA 0	ss-IGA 0/1[a]	ss-IGA 0[a]	PSSI 90	CMI in Scalp Itch NRS	sPGA-G 0/1[a]	sPGA-G 0[a]	SFQ 0/1	CMI in GPSS Genital Itch NRS	Hf-PGA 0/1[a]
Placebo	6	1	11	2	6	9	21	10	36	13	26
Icotrokinra 200 mg QD	57 (Δ+51.1)	25 (Δ+24)	66 (Δ+55)	49 (Δ+47)	57 (Δ+51)	59 (Δ+50)	77 (Δ+56)	62 (Δ+52)	80 (Δ+44)	64 (Δ+51)	42 (Δ+16)

*Primary Endpoint. All values represent percentages unless stated otherwise. **Orange** numbers in parentheses show the difference between icotrokinra and placebo for each stated endpoint.
CMI, clinically meaningful improvement; hf-PGA, Physician's Global Assessment of hands and feet; ICO, icotrokinra; IGA, Investigator's Global Assessment; IGA 0/1, IGA score 0/1 & ≥2-grade improvement from baseline; NA, not available; NRS, Numeric Rating Scale; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsO, plaque psoriasis; PSSD, Psoriasis Symptoms and Signs Diary; PSSI, Percentage of Participants Achieving Psoriasis Scalp Severity Index (PSSI) 90; QD, once-daily; sPGA-G, static Physician's Global Assessment of Genitalia; ss-IGA, scalp-specific Investigator's Global Assessment.

Protagonist Therapeutics

1. Presented at the American Academy of Dermatology Annual Meeting, March 7-11, Orlando, FL. 2. Presented at the Society For Investigative Dermatology Annual Meeting, May 7-10, 2025, San Diego, CA; 3. Presented at the European Alliance of Associations for Rheumatology (EULAR) 2025; Barcelona, Spain; June 11–14, 2025.

Phase 3 ICONIC TOTAL Study: Safety Results Through Week 16[1]

Adverse Event Rates Generally Similar Between Groups

	ICO 200 mg QD (N=208)	PBO (N=103)
Mean weeks of follow-up	16.0	15.7
Any AE	104 (50%)	43 (42%)
Most common AEs (≥5%)		
Nasopharyngitis	26 (12%)	11 (11%)
Upper respiratory tract infection	9 (4%)	5 (5%)
Headache	6 (3%)	6 (6%)
SAE[a]	1 (<1%)	2 (2%)
Infection	59 (28%)	22 (21%)
Serious infection	0	1 (1%)
AE leading to discontinuation[b]	4 (2%)	3 (3%)
Gastrointestinal AE	15 (7%)	8 (8%)
Active TB	0	0
Malignancy[c]	1 (<1%)	0

[a]SAEs through Week 16 included COVID-19 pneumonia, sepsis, sciatica, and acute respiratory failure in the PBO group; and hepatitis in the ICO group. [b]AEs leading to discontinuation through Week 16 included COVID-19 pneumonia, psoriatic arthropathy, and psoriasis in the PBO group; and vision blurred, visual field defect, laryngitis fungal, malignant melanoma in situ, and headache in the ICO group. [c]Malignancy reported in the ICO group was malignant melanoma in situ in a patient with a recent personal history of melanoma (in 2021). COVID-19, coronavirus disease 2019; ICO, icotrokinra; PBO, placebo; SAE, serious adverse event; TB, tuberculosis.

Protagonist Therapeutics

1. Presented at the Society For Investigative Dermatology Annual Meeting, May 7-10, 2025, San Diego, CA.

Phase 3 ICONIC-ADVANCE 1 and 2 Studies[1,2]

Week 16 Efficacy Summary: Co-Primary and Key Secondary Endpoints

- In the pivotal Phase 3 ICONIC-ADVANCE 1 & 2 studies, adults with moderate-to-severe plaque PsO receiving icotrokinra consistently demonstrated superior skin clearance and symptom relief vs placebo and deucravacitinib at Week 16

	Week 16											
	IGA 0/1*		PASI 90*		IGA 0		PASI 100		PSSD Symptom Score 0		CMI in PSSD Itch Score	
ICONIC-ADVANCE	**-1**	**-2**	**-1**	**-2**	**-1**	**-2**	**-1**	**-2**	**-1**	**-2**	**-1**	**-2**
Placebo	11	9	4	1	2	1	1	1	3	0	17	15
Icotrokinra 200 mg QD	68 **(Δ+57)** **(Δ+18)**	70 **(Δ+61)** **(Δ+16)**	55 **(Δ+51)** **(Δ+25)**	57 **(Δ+56)** **(Δ+23)**	37 **(Δ+35)** **(Δ+21)**	37 **(Δ+36)** **(Δ+20)**	31 **(Δ+30)** **(Δ+20)**	32 **(Δ+31)** **(Δ+18)**	24 **(Δ+21)** **(Δ+15)**	21 **(Δ+21)** **(Δ+8)**	62 **(Δ+45)** **(Δ+8)**	60 **(Δ+45)** **(Δ+9)**
Deucra 6 mg QD	50	54	30	34	16	17	11	14	9	13	54	51

*Co-primary endpoints. CMI, clinically meaningful improvement (≥4-point improvement from baseline); Deucra, deucravacitinib; IGA, Investigator's Global Assessment; IGA 0/1, IGA score 0/1 & ≥2-grade improvement from baseline; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptoms and Signs Diary; QD, once-daily.
All values represent percentages. **Orange** numbers in parentheses show the difference between icotrokinra and placebo. **Purple** numbers in parentheses show the difference between icotrokinra and deucravacitinib for each stated endpoint.

Protagonist Therapeutics

1. Presented at the European Academy of Dermatology and Venerology Meeting, September 17-20, 2025, Paris, France. 2. Presented at the Fall Clinical Dermatology Conference (FCDC) 2025; Las Vegas, NV, USA; October 23–26, 2025.

ICONIC-ADVANCE 1 and 2: No ICO Safety Signal Observed Through Week 24[1,2]

ICO Infection Rates Comparable to PBO Through Week 16 and Lower Than Deucra Through Week 24

Combined ICONIC-ADVANCE 1 & 2 AEs[a]	Placebo-Controlled (Week 0 to 16)			Active Comparator-Controlled (Week 0 to 24)	
	PBO (N=237)	ICO (N=632)	Deucra (N=634)	ICO (N=632)	Deucra (N=634)
Mean weeks/total PY of follow-up	15.5 / 70.5	15.9 / 192.7	15.8 / 191.6	23.6 / 285.2	23.3 / 283.1
Most common AEs (≥5%[b])					
Infection	73 (31%)	145 (23%)	202 (32%)	190 (30%)	253 (40%)
Incidence/100 PY (95% CI)[c]	128 (94, 151)	86 (72, 100)	130 (111, 147)	80 (69, 92)	118 (104, 133)
Nasopharyngitis	13 (5%)	37 (6%)	58 (9%)	56 (9%)	77 (12%)
Upper respiratory tract infection	8 (3%)	23 (4%)	33 (5%)	32 (5%)	49 (8%)
Headache	11 (5%)	26 (4%)	19 (3%)	28 (4%)	20 (3%)
Gastrointestinal AEs[d]	15 (6%)	45 (7%)	63 (10%)	55 (9%)	80 (13%)
Incidence/100 PY (95% CI)[c]	22 (12, 38)	24 (17, 32)	35 (26, 44)	20 (15, 26)	31 (24, 37)
Other AEs of Interest					
Acne[e]	0	4 (1%)	27 (4%)	5 (1%)	30 (5%)
Herpes[f]	6 (3%)	5 (1%)	13 (2%)	6 (1%)	18 (3%)

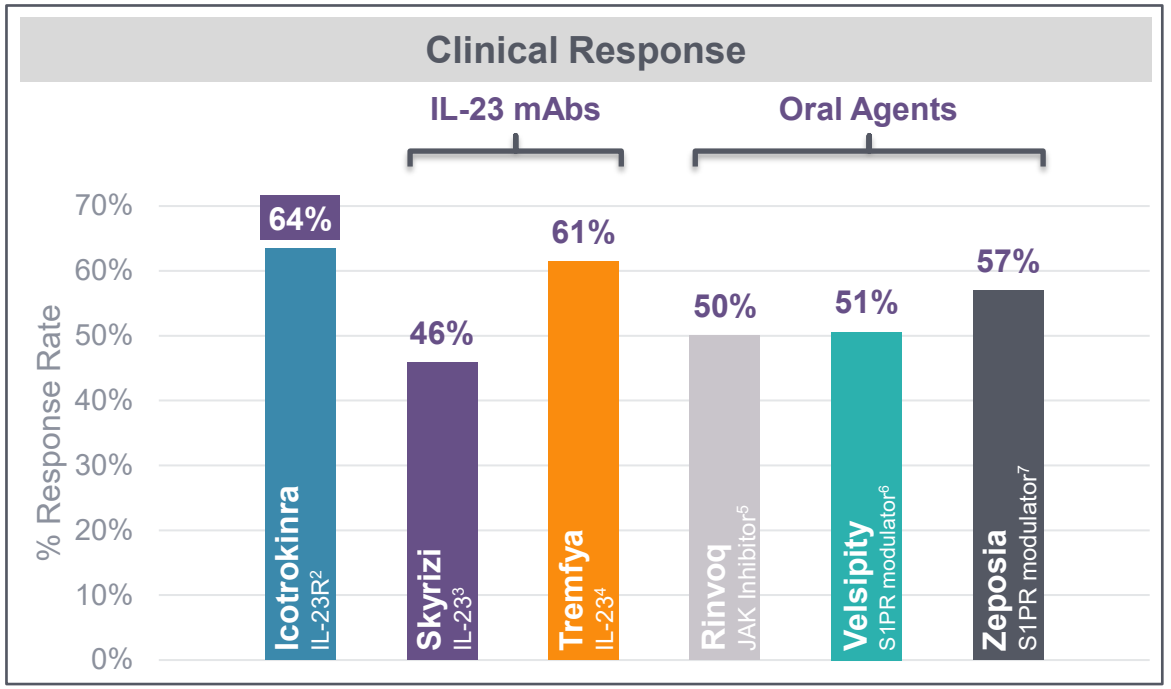
Values are n (%) unless otherwise noted. [a]Safety analysis set included all randomized and treated participants (pts); ICONIC-ADVANCE 1 & 2: PBO, 155/82; ICO, 310/322; Deucra, 307/327. [b]Pts in any treatment group. [c]Incidence/100 PY: number of pts with AEs/total PY at risk × 100; CI based on study-size adjusted Wald statistics. [d]Based on gastrointestinal disorders SOC. [e]Included PTs acne, acne pustular, dermatitis acneiform. [f]Included PTs genital herpes simplex, herpes simplex, herpes virus infection, herpes zoster, oral herpes.
AE, adverse event; CI, confidence interval; Deucra, deucravacitinib; ICO, icotrokinra; PBO, placebo; PT, preferred term; PY, participant-years; SOC, system organ class; W, week.

Protagonist Therapeutics

1. Presented at the European Academy of Dermatology and Venerology Meeting, September 17-20, 2025, Paris, France. 2. Presented at the Fall Clinical Dermatology Conference (FCDC) 2025; Las Vegas, NV, USA; October 23–26, 2025.

Icotrokinra Cross-Trial Comparison to Phase 2 Benchmarks in UC[1]

Clinical Response



Agent	Endpoint Timeframe	Placebo Response (%)
Icotrokinra	**Wk 12**	**27.0**
Skyrizi	Wk 12	20.0
Tremfya	Wk 12	27.6
Rinvoq	Wk 8	13
Velsipity	Wk 12	32.5
Zeposia	Wk 8	37

1. Cross trial (not head-to-head) comparisons of unadjusted (ie, non-placebo adjusted) response data from phase 2 studies.
2. Icotrokinra (JNJ-2113) highest dose (in mg; PO qd) with clinical response at Wk 12 (ie, decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1). Clinical response (placebo): 27.0%. Protagonist Therapeutics, Inc. "Protagonist Reports Positive Top Line Results from Phase 2b Study of Icotrokinra Showing Potential to Transform the Treatment Paradigm for Patients with Ulcerative Colitis." News release. 10 March 2025.
3. Skyrizi 1200 mg IV (approved dose; phase 2 data) clinical response per Adapted Mayo score at Wk 12 (ie, decrease of ≥30% and ≥2 points from baseline and a decrease in rectal bleeding score of ≥1 or an absolute rectal bleeding score ≤1). Clinical response score (placebo): 20.0%. Louis E, et al., *JAMA*. 2024;332:881-97.
4. Tremfya 200 mg IV (approved dose; phase 2 data) clinical response at Wk 12 (ie, decrease in modified Mayo score from baseline by ≥30% and ≥2 points, with either a ≥1-point decrease from baseline in the rectal bleeding subscore or a rectal bleeding subscore of 0 or 1). Clinical response (placebo): 27.6%. Peyrin-Biroulet L, et al., *Gastroenterology*. 2022;165:1443-57.
5. Rinvoq 45 mg PO QD (approved dose; phase 2 data) with clinical response at Wk 8 (ie, adapted Mayo score; defined as a decrease from baseline in the adapted Mayo score of 2 points and 30% from baseline, plus a decrease in rectal bleeding score of 1 or an absolute rectal bleeding score of 1). Clinical response (placebo): 13%. Sandborn WJ, et al., *Gastroenterology*. 2020;158:2139-49.
6. Velsipity 2 mg PO QD (approved dose; phase 2 data) with clinical response at Wk 12 (ie, met the criteria for clinical remission or had a decrease in modified Mayo Clinic score of 2 points and a decrease of 30%, with either a rectal bleeding score of 1 or a decrease in rectal bleeding of 1). Clinical response (placebo): 32.5%. Sandborn WJ, et al., *Gastroenterology*. 2020;158:550-61.
7. Zeposia 1 mg PO QD (approved dose; phase 2 data) with clinical response at Wk 8 (ie, reduction in the Mayo Clinic score of ≥3 points and ≥30% from baseline, with a decrease in the rectal-bleeding subscore of ≥1 point or a subscore of ≤1). Clinical response (placebo): 37%. Sandborn WJ, et al., *New Engl J Med*. 2016;18:1754-62.

Protagonist Therapeutics

Icotrokinra

J&J and Protagonist Collaboration Economics

$387.5M
Upfront + milestones achieved to-date

$580M
future potential development and sales milestones

6%-10% Royalties
7.25% *weighted average at $4B annual sales*
10% *for annual sales ≥ $4B*

Potential Development milestones through 2028			Expected
Any indication	Receipt of marketing approval	$50M	~2026 ✓
Remaining milestones			
2nd indication	NDA filing acceptance	$25M	~2027
	Receipt of marketing approval	$45M	~2028
3rd indication	NDA filing acceptance	$35M	~2028
	Receipt of marketing approval	$50M	~2028-29
Total potential development milestones		**$155M**	

Icotrokinra Sales Milestones*	
Calendar Year Net Sales	Sales Milestone
$1 Billion	$70M
$2 Billion	$95M
$3 Billion	$160M
$5 Billion	$100M
Total Potential Sales Milestones	**$425M**

Illustrative royalties in peak sales year				
Annual net sales*	**$5.0B**	**$10.0B**	**$15.0B**	**$20.0B**
Pre-tax royalty receivable*	**$0.4B**	**$0.9B**	**$1.4B**	**$1.9B**

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*Sensitivity analysis purposes only and does not represent management guidance, expectations or projections

Rusfertide

Takeda and Protagonist Partnership Economics

Scenario	Total upfront + milestones	Upfront	Payable upon opt -out	Potential Milestones	Royalty Rates**	Comment
Opted-In	$630M	$300M	-	$330M	10%-17% Ex-US	50:50 US Profit/loss share
Opted-Out	$1,675M	$300M	**$400M***	**$975M**	**14%-29% worldwide****	Exclusive US rights to Takeda

- **Opted-out: April '26**
  - $200M payable upon opt-out and a further $200M upon FDA approval
- **Milestones (2026-28):** $75M upon FDA approval + $25M Ex-US approvals (opt-out scenario)
- **Royalties:**
  - **29% at ≥$1.5B net sales**
  - **21% weighted average royalty rate at $1.5B in net sales**

Illustrative royalties during peak sales year (Opt-out Scenario)				
Annual net sales* **	**$1.0B**	**$1.5B**	**$2.5B**	**$3.5B**
Pre-tax royalty receivable* **	**$0.2B**	**$0.3B**	**$0.6B**	**$0.9B**

Sales Milestones	
$250M	**$25M**
$500M	**$50M**
$1.0B	**$100M**
$1.5B	**$150M**
$2.0B	**$200M**
$2.5B	**$250M**
Total potential milestones	**$775M**

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* $200M payable upon opt-out and a further $200M upon FDA approval **excluding 1% payable to a third party *** Sensitivity analysis purposes only and does not represent management guidance, expectations or projections

Identifying PV Patients Who Will Benefit From Rusfertide

Defining patient population characteristics using current market treatments and trends is the key to understanding rusfertide's market opportunity

Key indicators of suboptimal control for a PV patient

Phlebotomy Frequency

A high frequency of phlebotomies indicates the intervention is not working to maintain Hct ≤45%

Frequent phlebotomies may exacerbate iron deficiency and related symptoms[1]

Dosing of Hydroxyurea

High doses of HU (1-2 g/day) can indicate difficult-to-control PV, especially when used in combination with phlebotomy

Potential serious side effects and adverse events, including leukemic transformation and skin malignancies[2]

Thrombotic Events

Occurrence of thrombotic events following treatment initiation can be an indicator of the ineffectiveness of the treatment – an example of a sub-optimally controlled PV patient

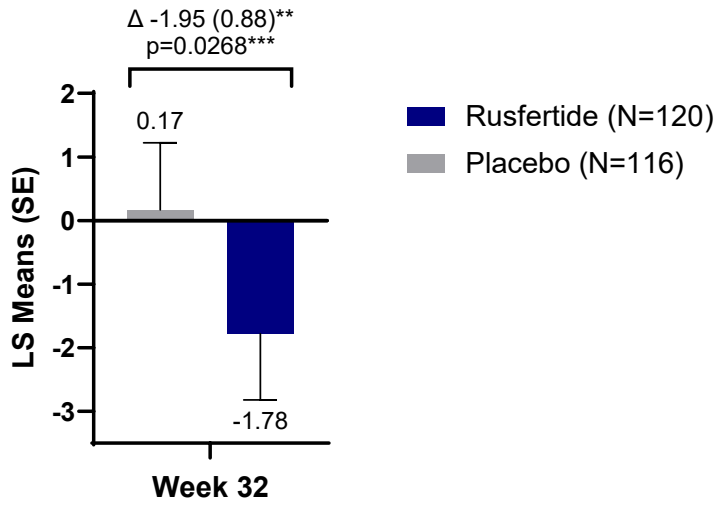
1. McMullin MF, et. al. *Br J Haematol*. 2019; 184(2):176-191. 2. Jinna S and Khandar PB. NIH 2022. https://www.ncbi.nlm.nih.gov/books/NBK537209/. 3. Stegelmann F, et al. *Leuk.* 2021;35(2):628-631.

Rusfertide Led to Statistically Significant Improvements In Patient-Reported Outcomes (PROs) vs Placebo[1,2]

PRO-Focused Key Secondary Endpoints 3 and 4

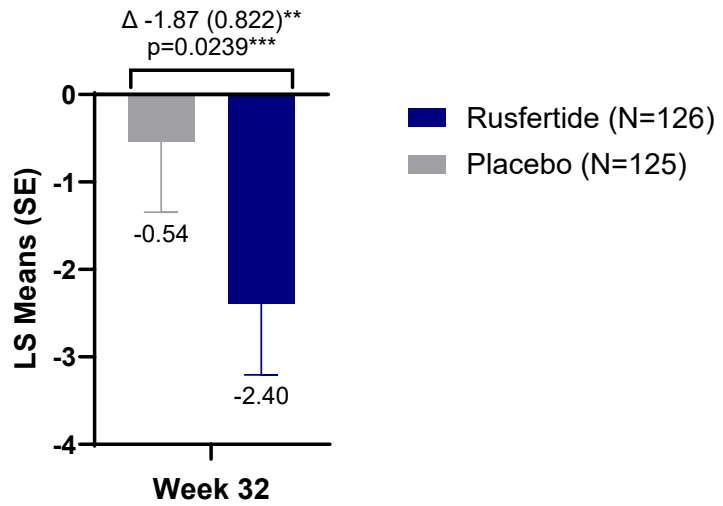
Improvement in PROMIS Fatigue SF-8a T-Score With Rusfertide vs Placebo

LS Means Difference at Week 32:



Improvement in MFSAF TSS7 With Rusfertide vs Placebo

LS Means Difference at Week 32:



**LS means (SE) difference (rusfertide – placebo); ***p-value associated with the LS means difference.
LS, least-squares; MFSAF TSS7, Myelofibrosis Symptom Assessment Form Version 4.0 Total Symptom Score 7 Items; PROMIS, Patient-Reported Outcomes Measurement Information System; SF-8a, Short Form 8a; SE, standard error.

1. Kuykendall AT et al. *J Clin Oncol* 2025;43(17_suppl):LBA3; 2. Kuykendall AT et al. *Blood* 2025;146(Suppl 1):81.

Rusfertide

A Potential New Treatment Option For Polycythemia Vera

PDUFA Date
Q3 '26

- PV is a rare myeloproliferative neoplasm characterized by excessive production of red blood cells[1]
  - Elevated hematocrit (Hct) >45%[2]
  - Primary treatment goal is to maintain Hct <45%[3,4]

HEMATOLOGY

Protagonist Therapeutics

RUSFERTIDE
Hepcidin Mimetic

Discovery/Pre-Clinical	Phase 1	Phase 2	Phase 3	Key Milestones	References
Polycythemia Vera (PV)					
VERIFY Ph 3, n = 293				• Topline 32-Wk Primary EP results • 52-Wk durability of response results	• Kuykendall AT et al. *J Clin Oncol* 2025;43(LBA3). • Kuykendall AT et al. *Blood* 2025;146(Suppl 1):81.
REVIVE Ph 2, n = 70				• Completed	• Kremyanskaya M, et al. *New Engl J Med* 2024;390:723-35.
THRIVE LTE, n = 46				• Ongoing; for REVIVE patients (OLE)	• Pemmaraju N, et al. *Blood* 2025;146(Suppl 1):3810.
PACIFIC Ph 2, Elevated Hct (>48%), n = 20				• Completed	• Chew LP, et al. *Leuk Res* 2025;159:108132.

Rusfertide has **Orphan Drug** designation, **Fast Track** status,
Breakthrough Therapy and Priority Review Designations

Hct, hematocrit; OLE, open-label extension.

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; 4. Barbui, T, et al. *Leukemia* 2018;32;1057-69

Rusfertide for Polycythemia Vera

Successful Completion of Phase 2 and 3 Studies

- Phase 2 **REVIVE** Study (N=70)[1-5]:
  - Randomized withdrawal data presented at EHA 2023[1] (late-breaking oral presentation); data published in *NEJM*[2]
- Phase 2 **THRIVE** Study (N=46)[6]:
  - Long-term extension study (for REVIVE patients on study years 3-5)
- Phase 2 **PACIFIC** Study (N=20)[7]:
  - High hematocrit (Hct >48%); 52-week open-label study completed in Q2 2023; data published in *Leuk Res*
- Phase 3 **VERIFY** Study (N=293)[8-11]
  - Primary endpoint and all four key secondary endpoints achieved in March 2025[8]
  - Data presented in plenary presentation at ASCO'25;[9] data included in NDA and will also be included in future regulatory filings (eg, MAA)
  - 52-week durability of response data presented at ASH'25[10]; additional data on PROs also presented at ASH'25[11]

Rusfertide has **Orphan Drug** designation, **Fast Track** status, and **Breakthrough Therapy** designation

1. Kremyanskaya et al. EHA2023; Abstract LB2710; 2. Kremyanskaya M, et al. *New Engl J Med*;2024;390:723-35; 3. Ritchie EK, et al. *Blood*. 2023;142 (Supplement 1): 745; 4. Pettit K, et al. EHA Library. 06/13/2024; 422322; S218; 5. Gerds, AT et al. *Blood* 2024;144 (Suppl. 1):4559; 6. Pemmaraju N, et al. *Blood* 2025;146(Suppl 1):3810; 7. Chew LP, et al. *Leuk Res;* 2025;159:108132. Epub ahead of print; 8. Takeda and Protagonist Therapeutics, Inc. "Protagonist and Takeda Announce Positive Topline Results from Phase 3 VERIFY Study of Rusfertide in Patients with Polycythemia Vera." News release. 3 March 2025; 9. Kuykendall AT et al. *J Clin Oncol* 2025;43(17_suppl):LBA3; 10. Kuykendall AT et al. *Blood* 2025;146(Suppl 1):81; 11. Bankar A, et al. *Blood* 2025;146(Suppl 1):5588.

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