Protagonist Therapeutics

# COMPANY OVERVIEW

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

January 12, 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 future results of operations and financial position; business strategy; our capital resources; pre-clinical and clinical product candidates (including PN-881, PN-477; PN-458 and PN-8047) and discovery programs; our icotrokinra collaboration with Johnson & Johnson Innovation, Inc. (”JNJ”) and our rusfertide collaboration with Takeda, including our expectations related to the achievement and timing of milestone and royalty payments from JNJ and Takeda; the potential market opportunities for icotrokinra and rusfertide and other product candidates; the impact on our business or product candidates of actions of the U.S. Food and Drug Administration (“FDA”) and foreign regulatory agencies, including expectations regarding timing of FDA approval of NDAs for icotrokinra and rusfertide; expectations regarding timing and announcements related to pre-clinical and clinical programs; 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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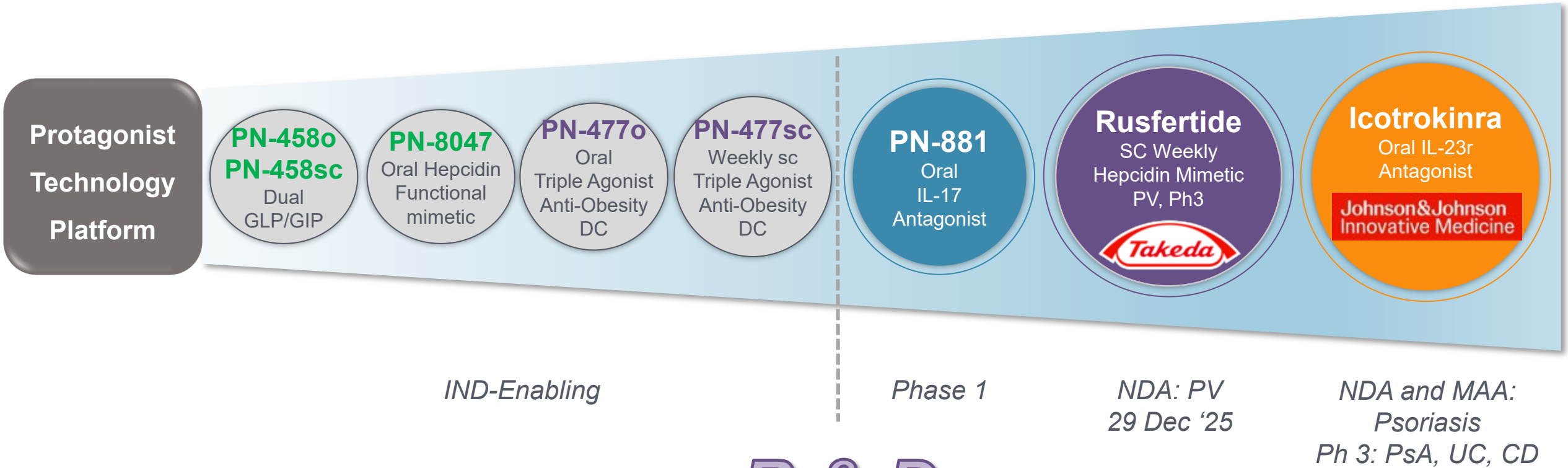
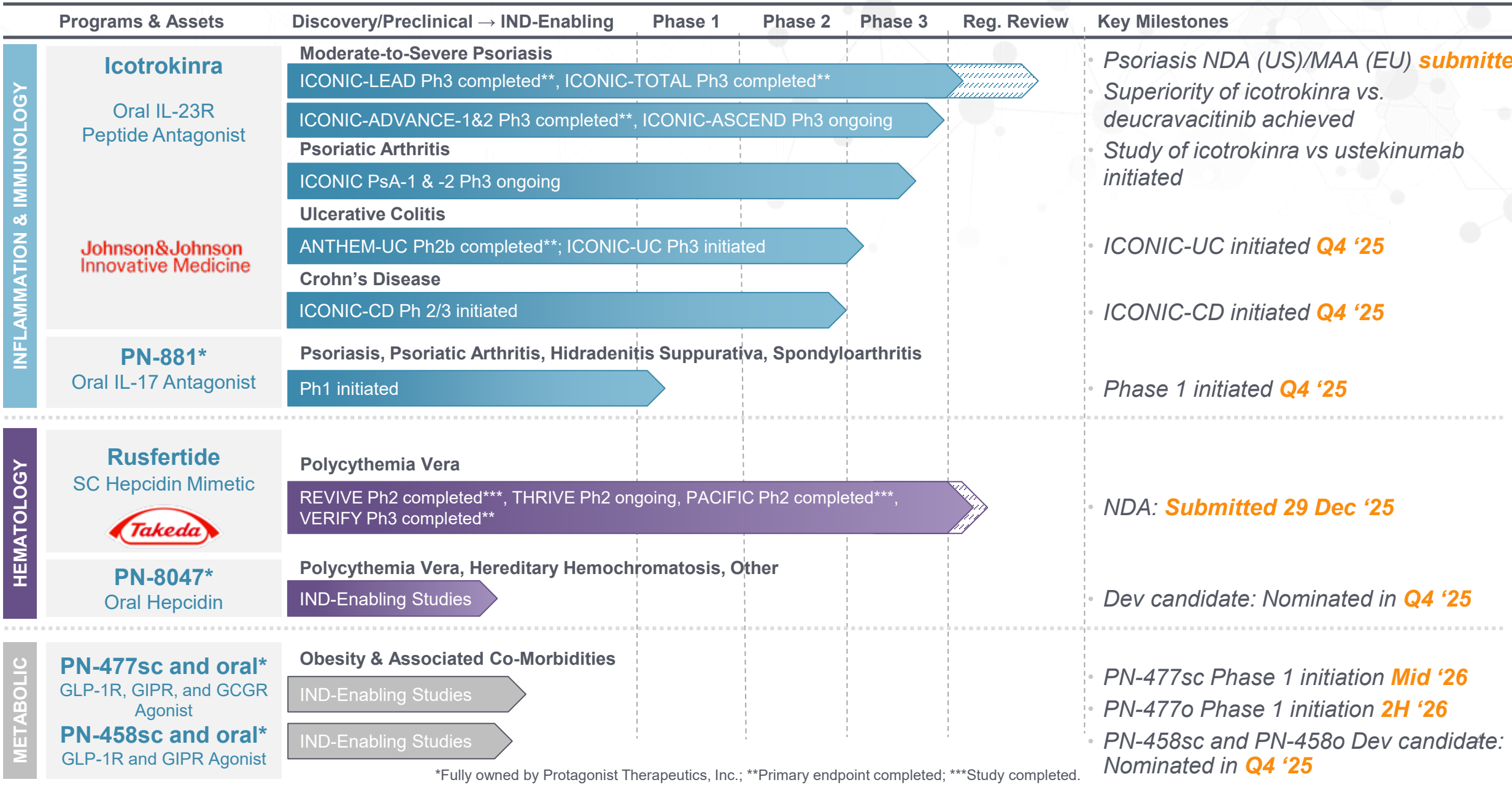
# Protagonist Therapeutics, Inc.

## Integrated Discovery and Development Company With a Validated Technology Platform

- Biologically and commercially validated targets
  - Immunology & inflammation, hematology, and metabolic diseases
- Strong differentiation vs existing therapies



# Pipeline of Proprietary and Partnered Programs




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

# Multiple Near-Term Catalysts

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

### Commercial Value Drivers

- ***Icotrokinra:*** First-in-class oral IL-23R antagonist
  - NDA filed for plaque psoriasis: July '25
  - MAA submitted Sep '25
  - 3 additional indications
- ***Rusfertide:*** First-in-class hepcidin hormone mimetic
  - NDA submitted for PV: Dec '25

### Multiple Clinical Programs I&I, Obesity and Hematology

- ***PN-881:*** Oral IL-17 antagonist
  - Ph1 completion
  - Ph2 psoriasis initiation
- ***PN-477sc:*** Triple-G, weekly sc
  - Ph1 initiation & data
- ***PN-477o:*** Triple-G, daily oral
  - Ph1 initiation

***New Development Candidates***

- ***PN-458sc & PN-458o:***
  - Dual GLP-1R/GIPR agonist
- ***PN-8047:***
  - Oral hepcidin functional mimetic

### 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 opportunistic share buybacks & dividends

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# Icotrokinra

## JNJ and Protagonist Collaboration Economics

**$337.5M**
*Upfront + milestones achieved to-date*

**$630M**
*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 |
| 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** | | **$205M** | |

| 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 |

- **Opt-out Optionality:** 90-day period beginning 120 days after NDA filing **(Q2/Q3 '26)**
  - $200M payable upon opt-out and a further $200M upon FDA approval
- **Milestones (2026-28):** $75M upon FDA approval + $25M x-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** |

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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.

# Potential Sales Milestones: Icotrokinra and Rusfertide

## Up to $1.2 Billion Receivable

| 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** |

| Rusfertide Sales Milestones* | |
|---|---|
| Calendar Year Net Sales | Sales Milestone |
| $250M | $25M |
| $500M | $50M |
| $1B | $100M |
| $1.5B | $150M |
| $2.0B | $200M |
| $2.5B | $250M |
| **Total Potential Sales Milestones** | **$775M** |

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* All sales milestones EXCLUDED from current cash runway forecast.

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Johnson&Johnson Innovative Medicine

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

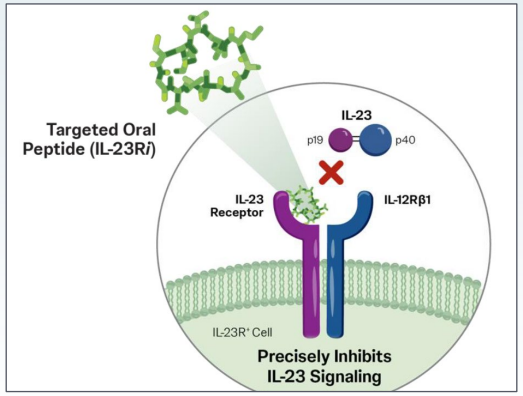
Setting a new standard of treatment in plaque psoriasis & other IL-23 mediated diseases

J&J Partnership: 2017 to Present

# 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® (ustekinumab) >$11B[2]

Tremfya® (guselkumab) >$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.

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# Icotrokinra Clinical Development Program

**Psoriasis NDA submitted July'25; MAA submitted Sept'25**

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

| | Reference(s) | Primary Endpoint Met? | Primary Endpoint Completion Date |
|---|---|---|---|
| **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. | ✓ | Dec '22 and Sept '23 |
| **ICONIC-LEAD[3]** Ph3, n = 684, in moderate-to-severe psoriasis | Bissonnette R, et al. *N Engl J Med.* 2025;393:1784-95. | ✓ | Jul '24 |
| **ICONIC-TOTAL[4]** Ph3, n = 311, psoriasis in special areas of body | Gooderham M, et al. *NEJM Evid.* 2025;Epub ahead of print. | ✓ | Jun '24 |
| **ICONIC-ADVANCE 1[5]** Ph3, n = 774, Icotrokinra vs. Deucravacitinib | Gold LS, et al. *Lancet.* 2025;406:1363-74. | ✓ | Sept '24 |
| **ICONIC-ADVANCE 2[6]** Ph3, n = 731, Icotrokinra vs. Deucravacitinib | | ✓ | Nov '24 |
| **Pustular/Erythrodermic Psoriasis[7]** Ph3, n = 19 | | | Jan '25 |
| **ICONIC-ASCEND[8]** Ph3, n = 752, Icotrokinra vs. Ustekinumab | | | ~Mar '26 |
| **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 | | ✓ | Dec '24 |
| **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 |

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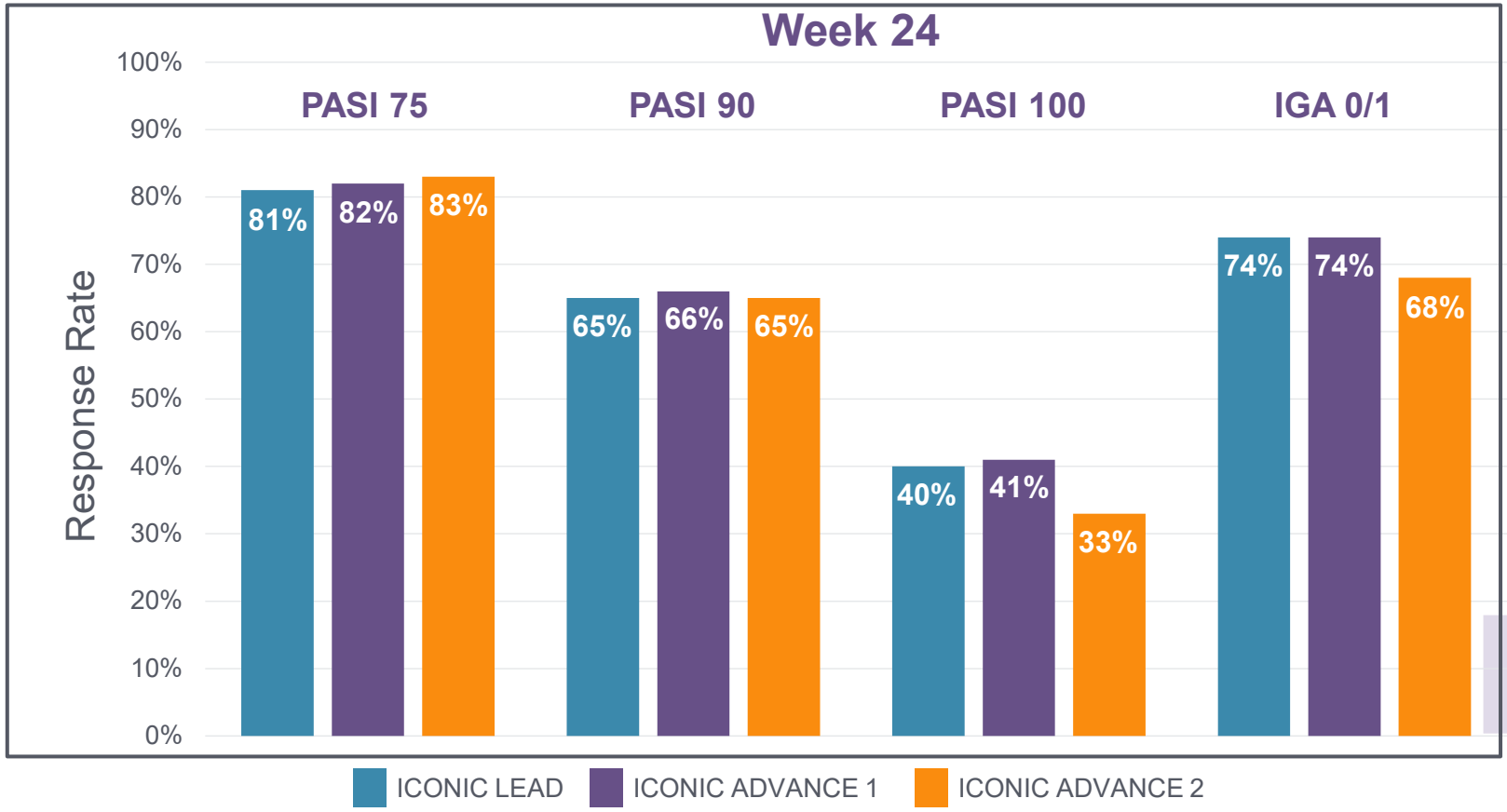
1. FRONTIER 1: NCT05223868
2. FRONTIER 2: NCT05364554
3. ICONIC-LEAD: NCT06095115
4. ICONIC-TOTAL: NCT06095102
5. ICONIC-ADVANCE 1: NCT06143878
6. ICONIC-ADVANCE 2: NCT06220604
7. Japan Ph3: NCT06295692
8. ICONIC-ASCEND: NCT06934226
9. ICONIC-PsA 1: NCT06878404
10. ICONIC-PsA 2: NCT06807424
11. ANTHEM-UC: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

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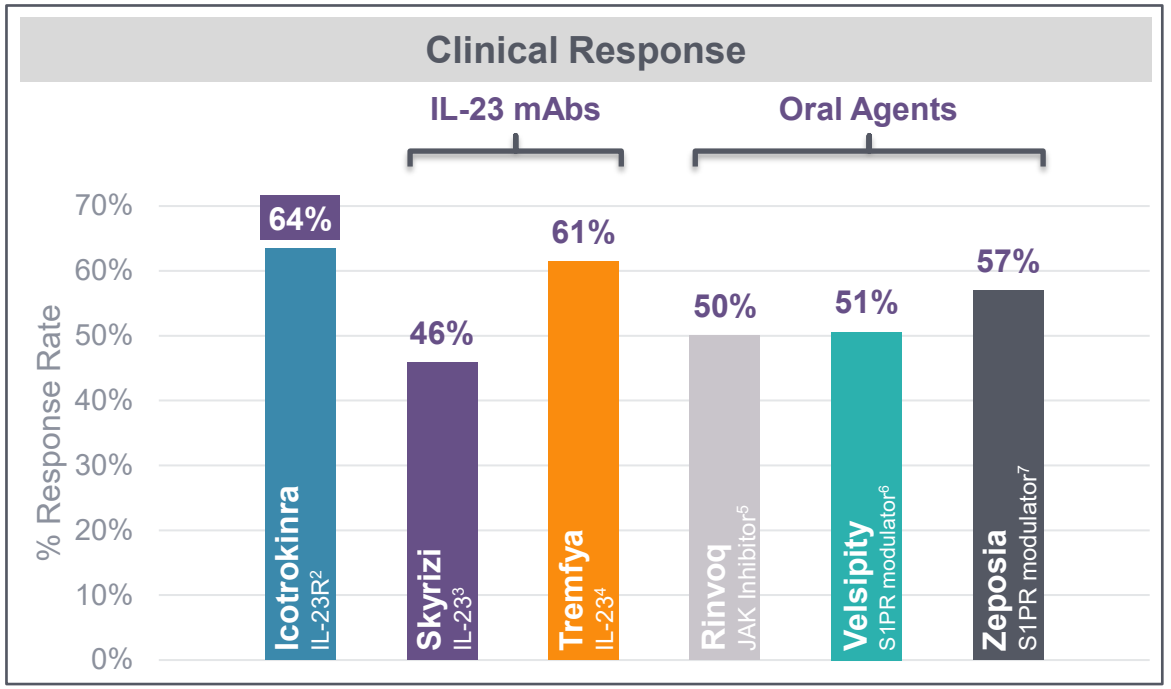
ICONIC LEAD NEJM Nov 2025; ICONIC ADVANCE 1&2 Lancet Sep 2025
PASI, Psoriasis Area and Severity Index. IGA, Investigator's Global Assessment;

# 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.

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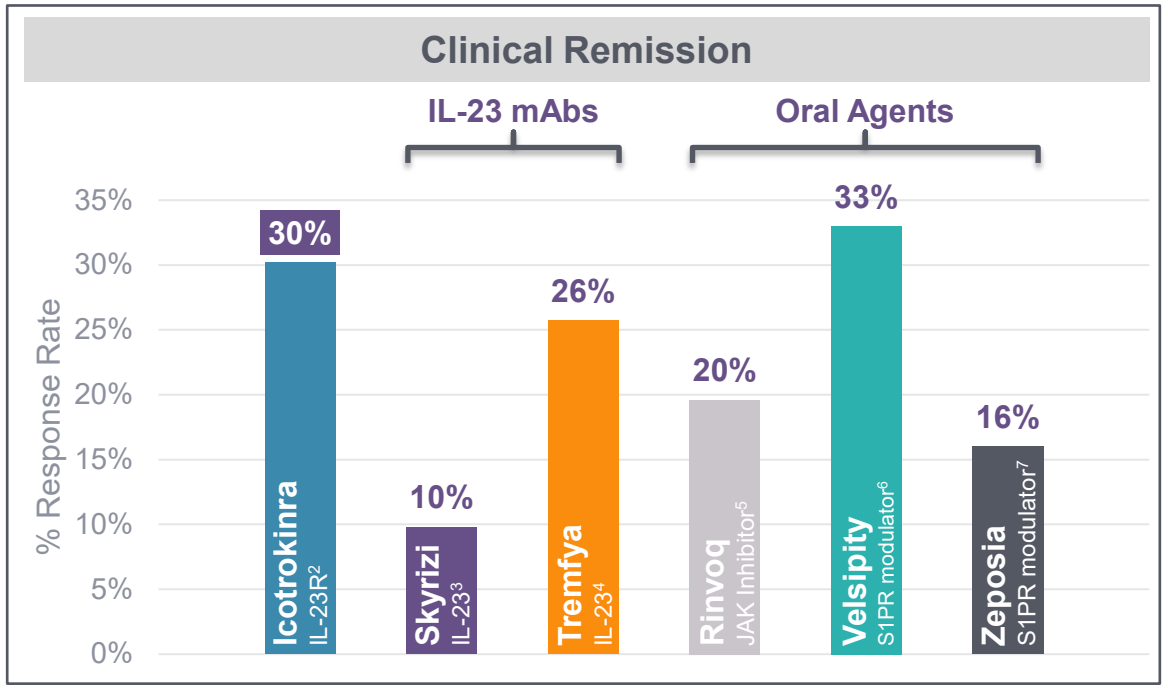
# Icotrokinra Cross-Trial Comparison to Phase 2 Benchmarks in UC[1]

## 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.

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# 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.

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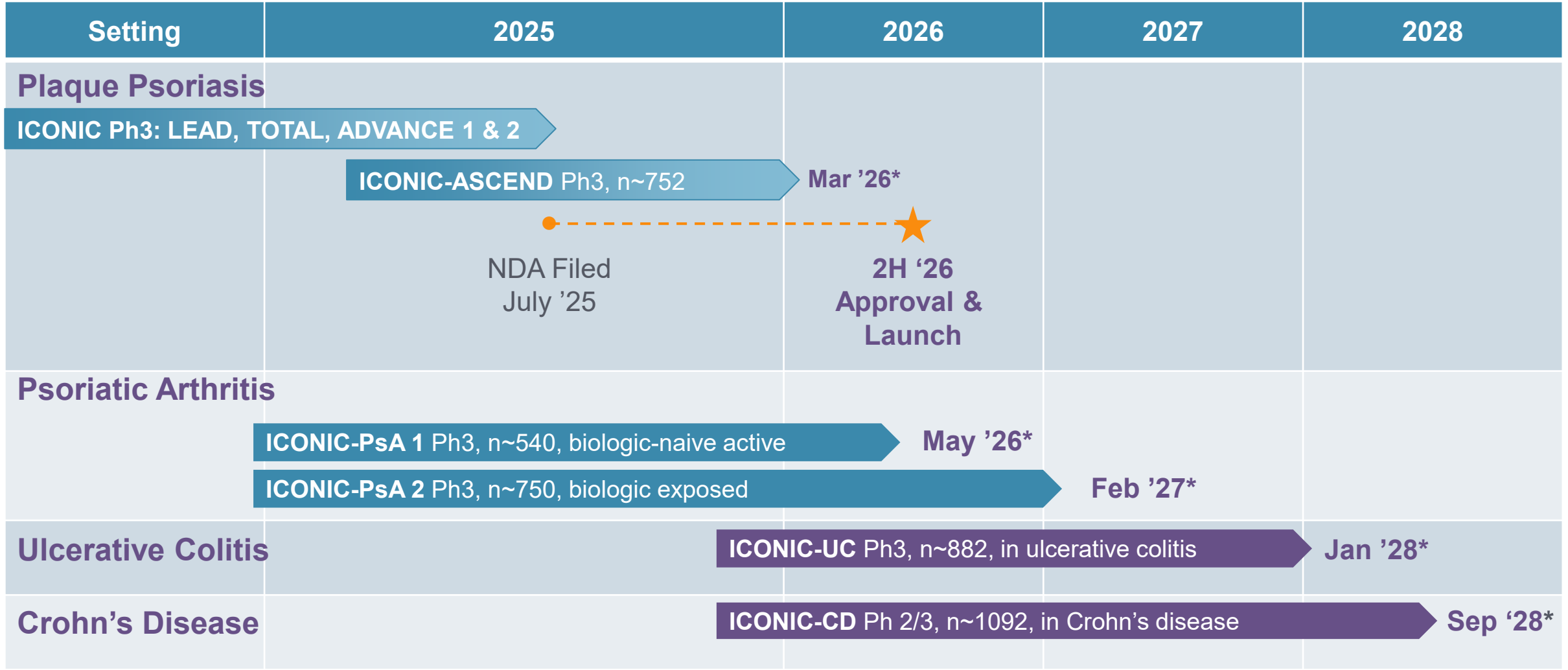
1. ClinicalTrials.gov. NCT07196748. Accessed on 30 September 2025.
2. ClinicalTrials.gov. NCT07196722. Accessed on 30 September 2025.

# Icotrokinra: Potential Commercial Launch in Psoriasis in 2026 followed by Multiple Indications Expansion in Coming Years

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* Primary Completion Date on clinicaltrials.gov

# 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]

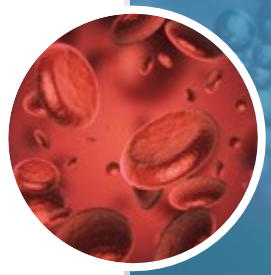

Polycythemia Vera. https://rarediseases.org/rare-diseases/polycythemia-vera/.
2. Spivak JL. *Ann Hematol* 2018; 19(2):1-14
3. Marchioli R, et al. *N Engl J Med* 2013; 368:22-33. 4. Barbui, T, et al. *Leukemia* 2018;32;1057-69

# Polycythemia Vera (PV)

## Disease Background

Rare myeloproliferative neoplasm characterized by excessive production of red blood cells (RBCs)[1]

- Elevated hematocrit (Hct) >45%[2]



Serious, chronic disease associated with increased thrombotic and cardiovascular risks[1-3]

~155,000 PV patients in US, with a median survival of 14 years[1,5]

**Primary Treatment goal is to maintain**

**Hct<45%**[3,4]


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
5. Tefferi A, Barbui T. *Am J Hematol*. 2023;98:1465-87.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# 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

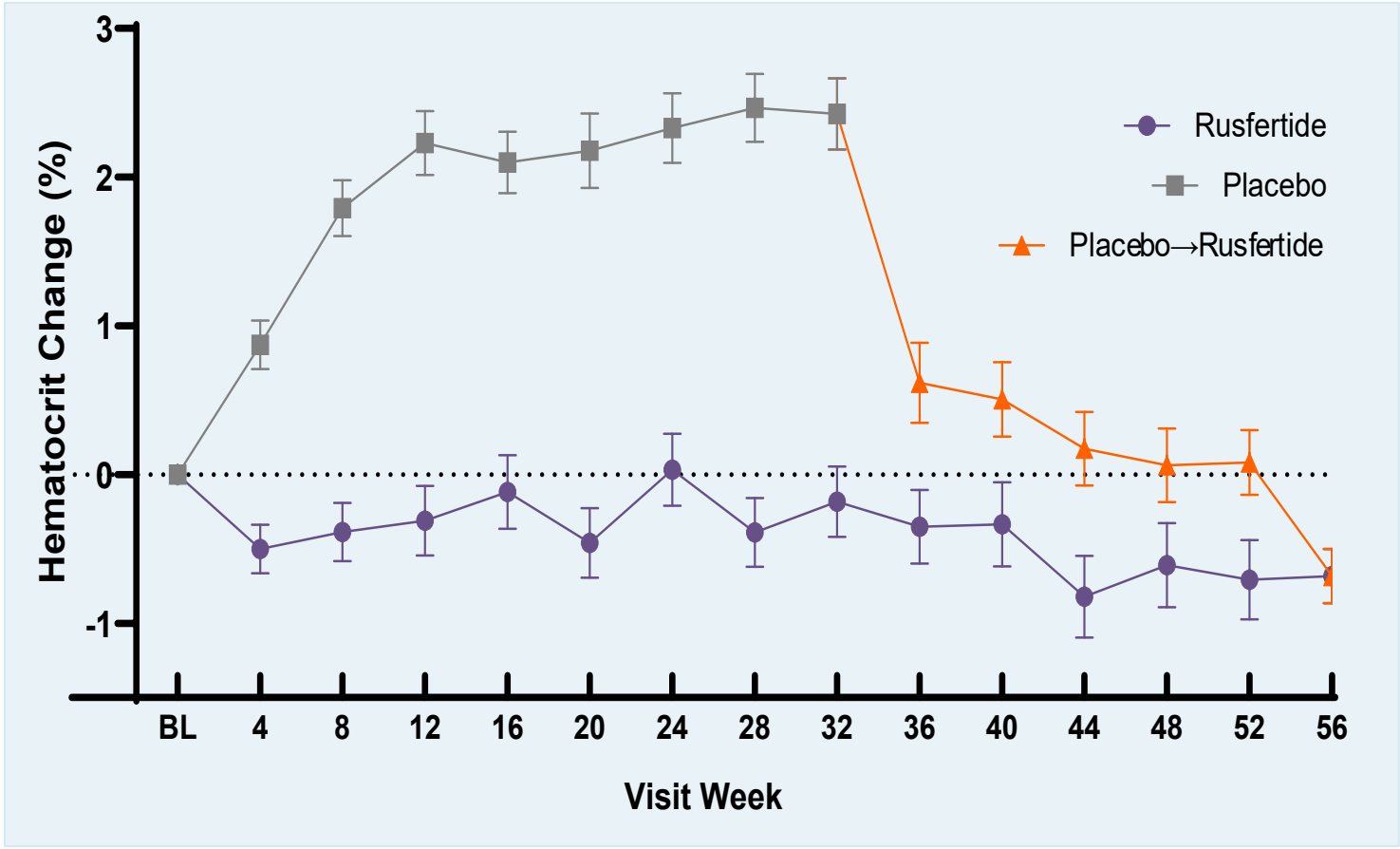
**Rusfertide, a hepcidin mimetic, could potentially provide an RBC-specific treatment option for PV**


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.

# 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: 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]**

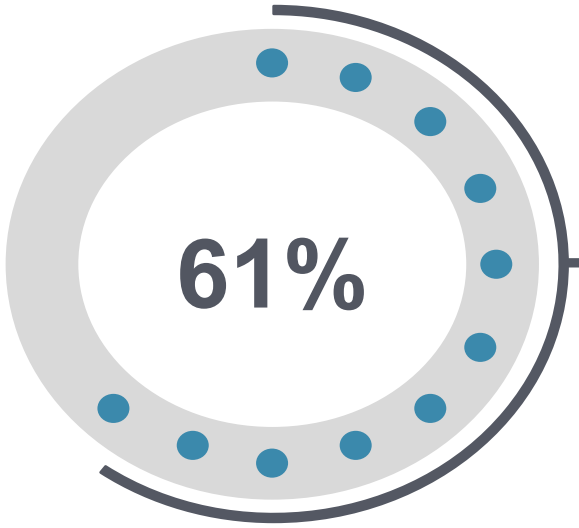
Rusfertide provides consistent hematocrit control and can potentially reduce treatment burden to achieve **peak revenue potential of $1-2B[3]**

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

## A Potential New Treatment Option For Polycythemia Vera

**Rusfertide NDA Submitted Dec '25**

- 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<br>• 52-Wk durability of response results | • Kuykendall AT et al. *J Clin Oncol* 2025;43(LBA3).<br>• 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. Epub ahead of print. |

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

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

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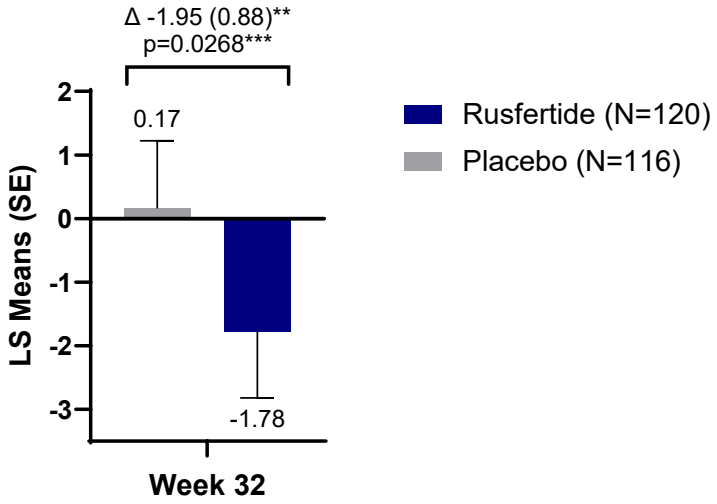
# Rusfertide Led to Statistically Significant Improvements In Patient-Reported Outcomes (PROs) vs Placebo[1,2]

## PRO-Focused Key Secondary Endpoints 3 and 4

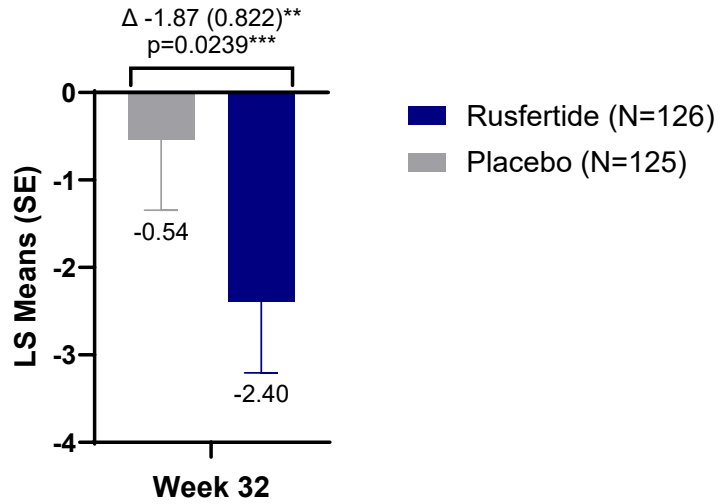
### Improvement in PROMIS Fatigue SF-8a T-Score With Rusfertide vs Placebo

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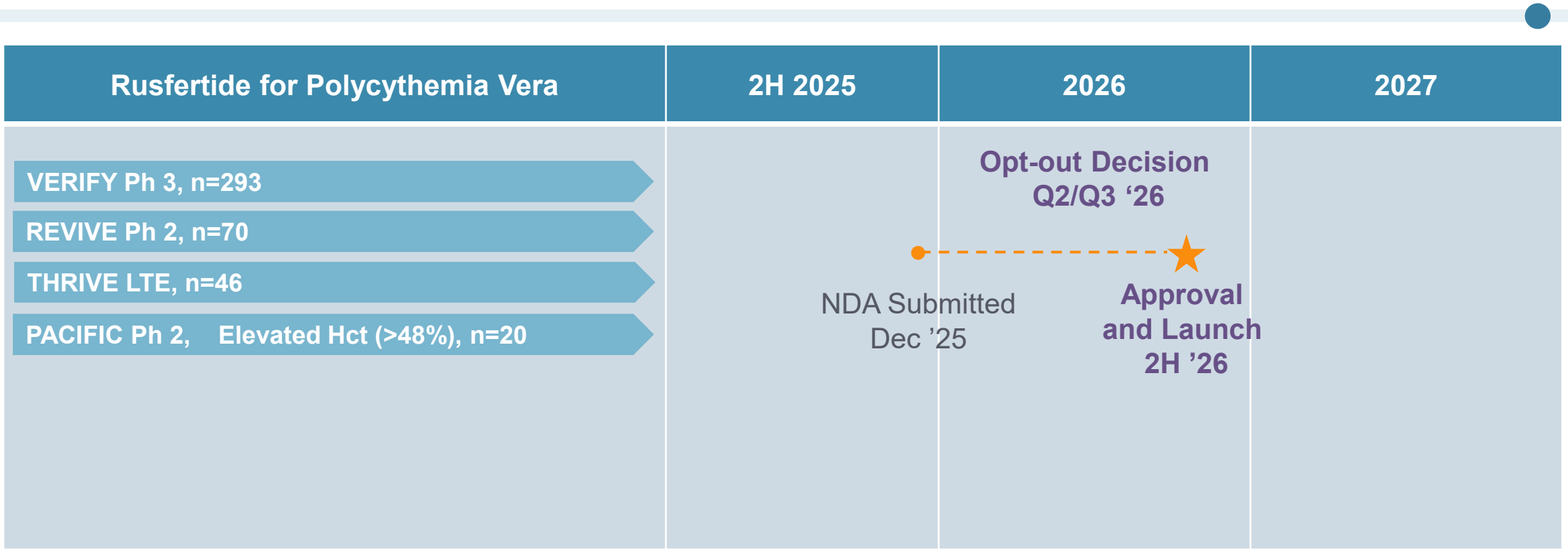
# Rusfertide for PV: NDA Filing, Approval and Commercialization Launch Timelines




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

Potential FDA approval and commercial launch in 2H 2026

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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

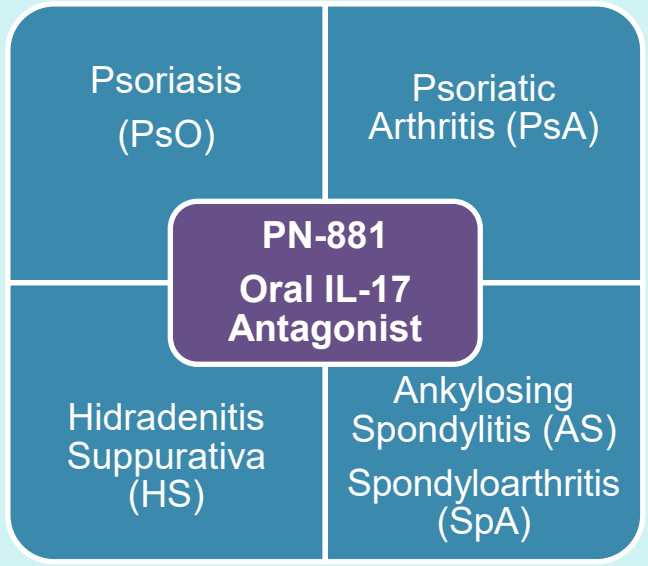
# Targeting a $17B+ Market Opportunity with Differentiated ORAL IL-17 Inhibition

## 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

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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<br>✓ Blocks all dimeric forms of IL-17: AA, AF, FF |
| Stability | ✓ Stable in simulated gastric and intestinal fluids<br>✓ Stable in serum with $t_{1/2}$ >24 hr<br>✓ Metabolic stability<br>✓ 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 |

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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.

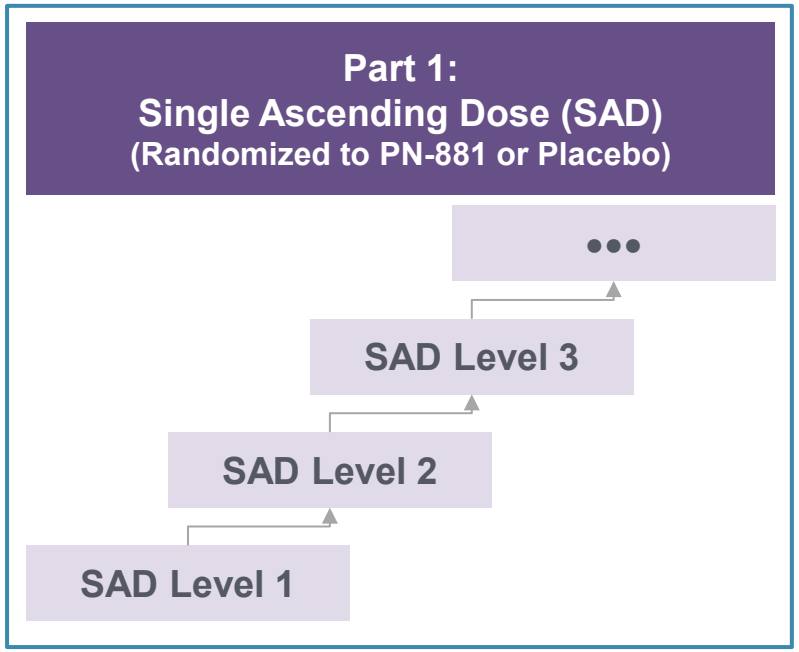
# PN-881 Achieves Desired Pharmacology in Preclinical Models

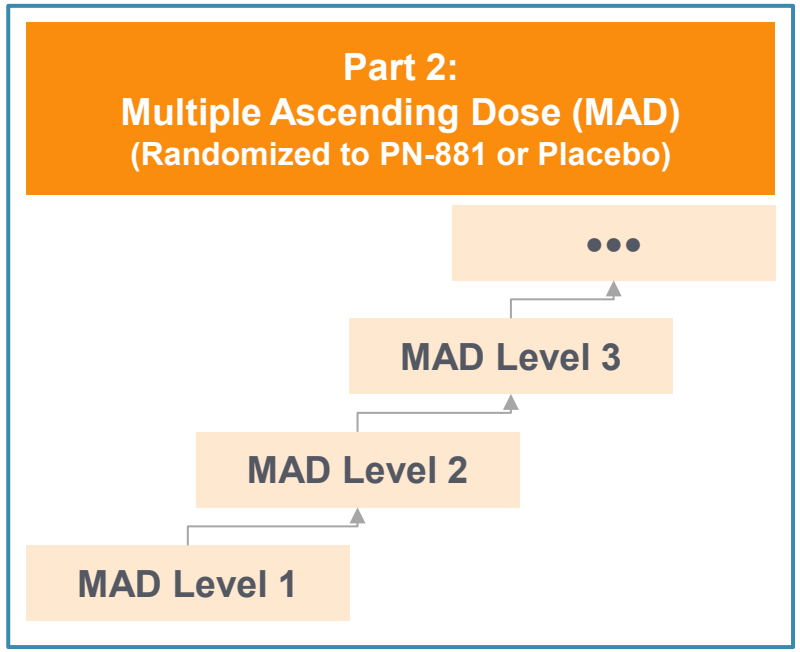
- High systemic exposures after oral administration to mice, rats, dogs, and cynomolgus monkeys
  - >100 ng/mL in cynomolgus monkeys with oral dose of 2.5 mg/kg

- 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**

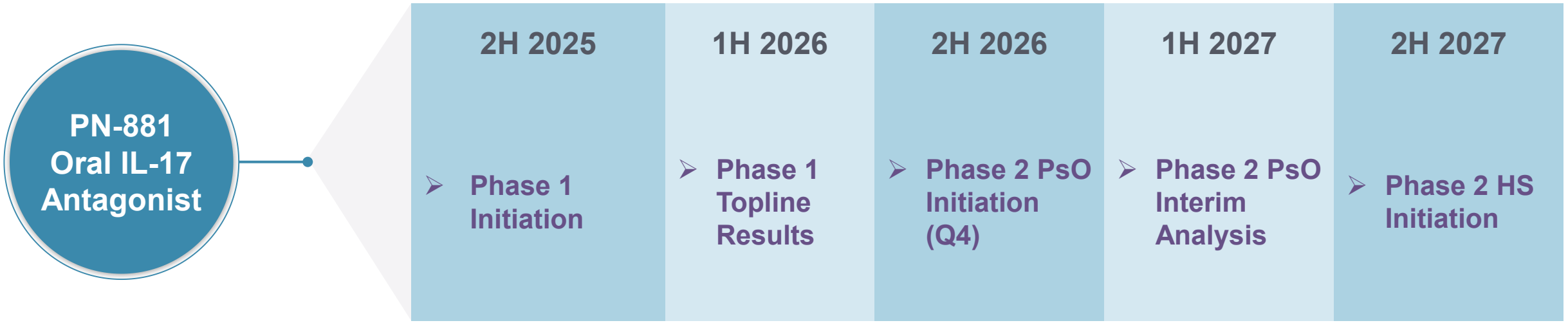
**Part 5:**
**Multiple Dose PK of Solid Dose Formulation**

- **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 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

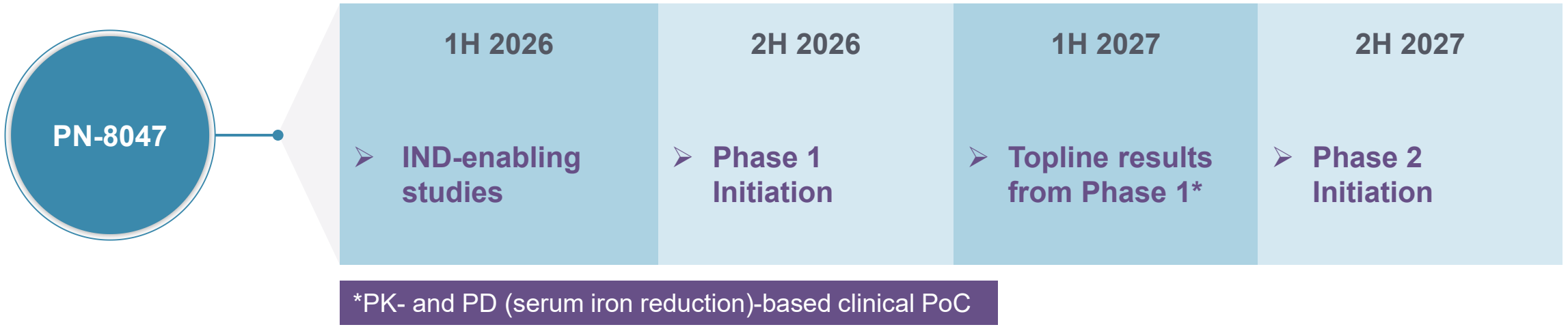
# PN-8047: Novel Oral Small Molecule that is Potent with Excellent PK, PD, and Efficacy Properties

| Attributes | Summary of PN-8047 Properties |
|---|---|
| Potency | ✓ Nanomolar potency in the T47D-TfR1 functional assay<br>✓ Similar potency as Rusfertide |
| in vitro ADME | ✓ Metabolically stable in liver microsomal incubations<br>✓ 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<br>✓ Sustained iron reduction for 16 hr |
| Efficacy Model | ✓ Efficacy in the erythropoietin (EPO)-induced mouse model for erythrocytosis<br>✓ Reduction of hemoglobin and hematocrit after repeat oral dosing to cynos |
| DDI | ✓ No DDI risk potential |
| Safety | ✓ No major off-target activities<br>✓ 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

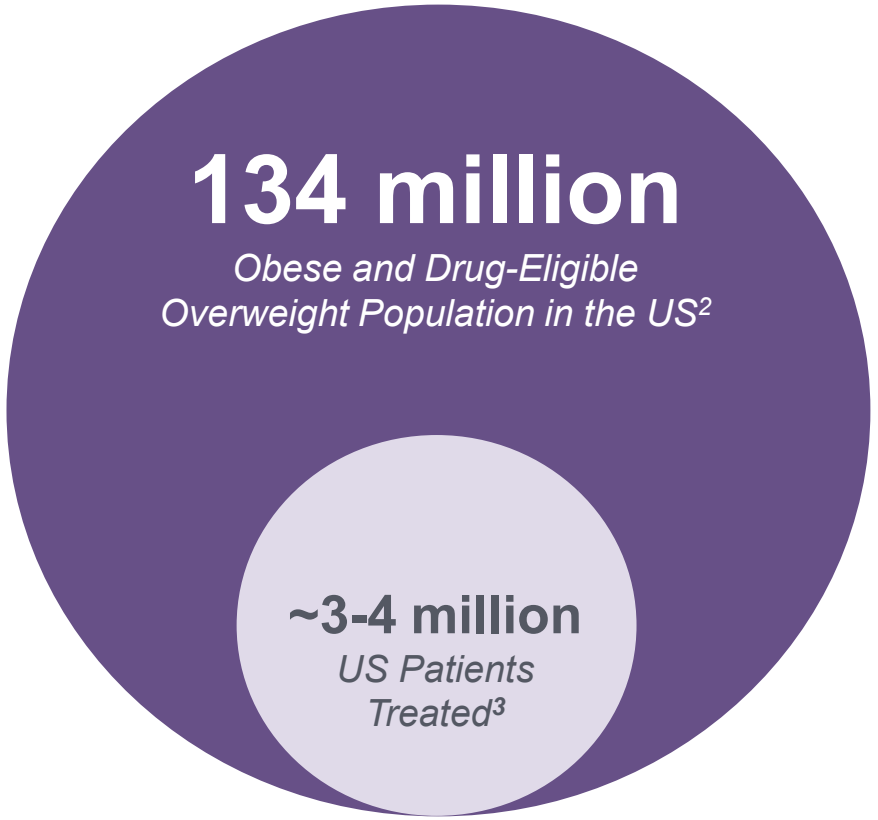
# Anti-Obesity Therapeutics: Dominated by injectable appetite-suppressing hormone peptide mimetics

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

# Obesity: Unprecedented Pharmaceutical Opportunity in the US and Worldwide

## Only ~2-3% 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[1]
- Current challenges with anti-obesity drugs[1]
  - 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]HSBC Research, Dec 2025 [2]Drug-eligible Population: obese (BMI≥30) and drug-eligible overweight (27≤BMI<30 with at least one weight-related comorbidity) Clarivate Disease Landscape & Forecast – Obesity/Overweight (March 2025). [3]Treated with GLP-1 RA for Obesity: IQVIA estimates, 2025; Novo Nordisk Earnings Call Nov 25

# 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]
- Retatrutide (injectable; triple agonist) and orforglipron (oral; mono GLP-1R agonist) in Ph3 development[3,4]

***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. Jastreboff AM, et al. Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial. *N Engl J Med* 2023;389:514-26; 4. Wharton S, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment. *N Engl J Med* 2025;393:1796-806.

# 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

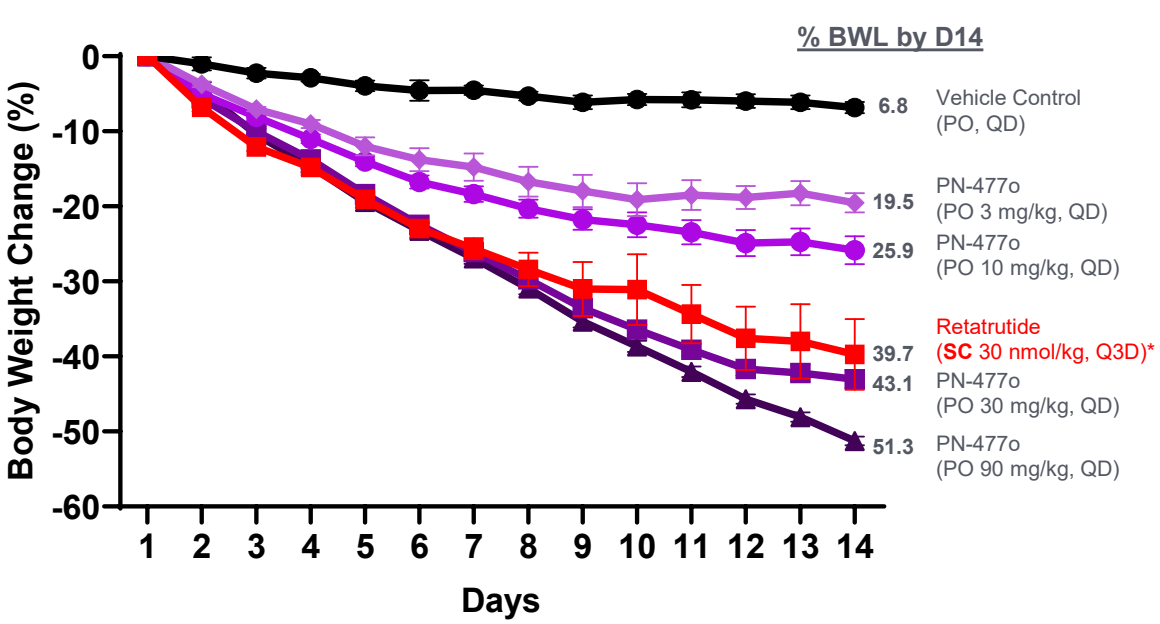
| Attribute | Criteria |
|---|---|
| Potency | ✓ nM potency vs GLP-1R, GIPR, GCGR |
| Stability | ✓ Stable in simulated gastric and intestinal fluids<br>✓ Stable in serum<br>✓ Metabolic stability<br>✓ Thermostability |
| Efficacy Model | ✓ Mouse Diet Induced Obesity (DIO) model |
| *in vivo* Pharmacodynamics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

GI: Gastrointestinal; PK: Pharmacokinetic

# Oral PN-477o and Subcutaneous PN-477sc

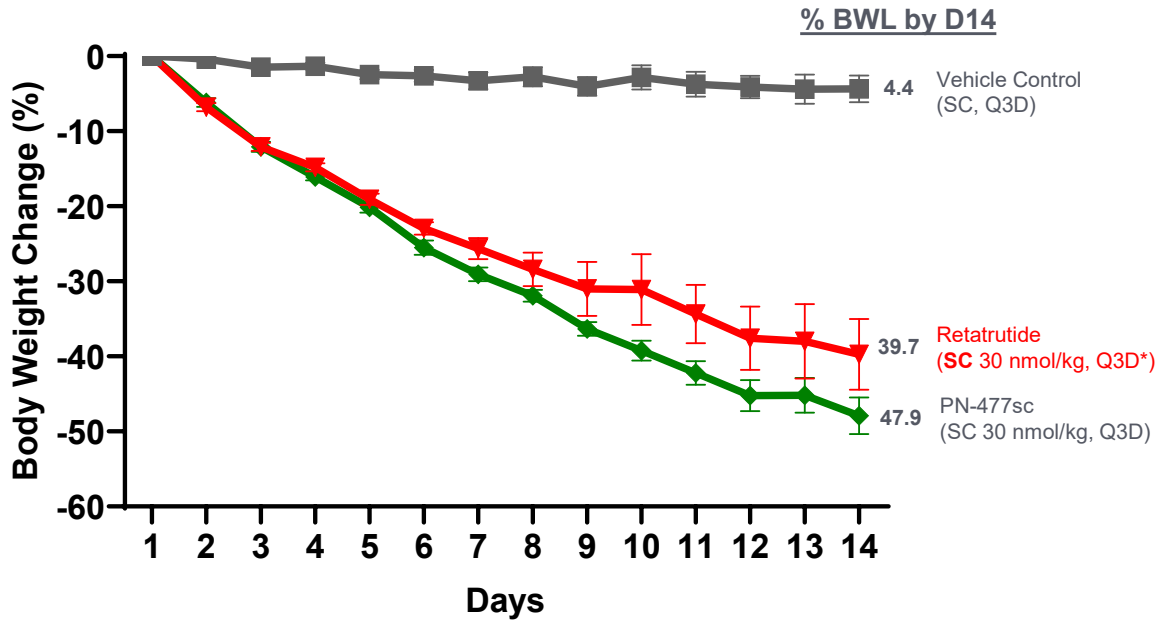
## DIO Mice Study #1

### % 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

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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 Development Candidate 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

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# PN-477: Near-Term Clinical Development Plan

**PN-477sc and PN-477o* Anti-Obesity**

| 1H 2026 | 2H 2026 | 1H 2027 | 2H 2027 |
|---|---|---|---|
| ➢ IND-enabling studies<br>➢ Phase 1 Initiation (sc) | ➢ Phase 1 Initiation (o) | ➢ Topline results from Phase 1 (sc)** | ➢ Topline results from Phase 1 (o) |

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

**Phase 1 study results could provide preliminary clinical PoC

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# 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 is higher potency than Tirzepatide for GLP-1R and GIPR
- Higher GIPR potency may be favorable for better GI tolerability[4,5]

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[1] Coskun T, Mol Metab 2018; [2] Coskun T, Cell Metab 2022; [4] Campbell JE, Cell Metabolism 2023; [5] 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<br>✓ Stable in serum<br>✓ Metabolic stability<br>✓ 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<br>✓ GI stability supports once-a-day oral dosing<br>✓ Plasma PK profile supports once-a-week subcutaneous dosing |

GI: Gastrointestinal; PK: Pharmacokinetic

***IND-enabling studies in progress***

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# 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**

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

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# What's Next?


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# Major Upcoming Catalysts in 2026-2027

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

| | 1H 2026 | 2H 2026 | 2027 |
|---|---|---|---|
| **Rusfertide** (Takeda) | ❖ NDA submitted | ❖ **Opt-in/Opt-out decision** | ❖ **US approval/launch for PV** ★ | ❖ Commercial |
| **Icotrokinra** (Johnson & Johnson Innovative Medicine) | ❖ Psoriasis NDA & MAA<br>❖ Ph3 PsA 1 & 2; UC & CD ongoing | ❖ Ph3 ICONIC-PsA 1 Primary Completion | ★ **US approval/launch for Psoriasis** | ❖ Commercial |
| **PN-881*** | Oral IL-17 antagonist<br>❖ Ph1 ongoing | ❖ Ph1 Topline<br>❖ PK/PD data | ❖ Ph2 PsO Initiation | ❖ Ph2 PsO Interim Analysis |
| **PN-477sc*<br>PN-477o*** | Anti-obesity DCs<br>❖ IND-enabling studies | ❖ PN-477sc Ph1 initiation | ❖ PN-477sc Ph1 clinical PoC<br>❖ PN-477o Ph1 initiation | ❖ Ph1 Topline |
| **PN-8047*** | ❖ Oral Hepcidin DC | | ❖ Ph1 initiation | ❖ Ph1 Topline |
| **PN-458sc*<br>PN-458o*** | Dual GLP/GIP DCs<br>❖ PN-458sc<br>❖ PN-458o | | ❖ Ph1 initiation | |
| **Discovery*** | ❖ AmylinR-based mono & poly-agonists<br>❖ Oral IL-4Rα antagonist | | |

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

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# Thank you