Protagonist Therapeutics

COMPANY OVERVIEW

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President & CEO

November 19, 2025

Forward-looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All statements other than statements of historical facts contained in this presentation, including statements regarding our future results of operations and financial position, business strategy, product candidates, capital resources, potential markets for our product candidates, our plans and expectations related to the impact on our business or product candidates of actions or determinations of the U.S. Food and Drug Administration ("FDA"), our collaboration with Johnson & Johnson Innovation, Inc. ("JNJ"), our collaboration with Takeda, our PN-881, obesity, and other discovery and pre-clinical programs including expectations regarding announcements related to those programs, our potential receipt of milestone payments and royalties under our collaboration agreements with JNJ and Takeda, and the timing of icotrokinra (JNJ-2113, formerly PN-235), Janssen's development plan for icotrokinra, and the potential market opportunity for rusfertide and icotrokinra, are forward-looking statements. 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.

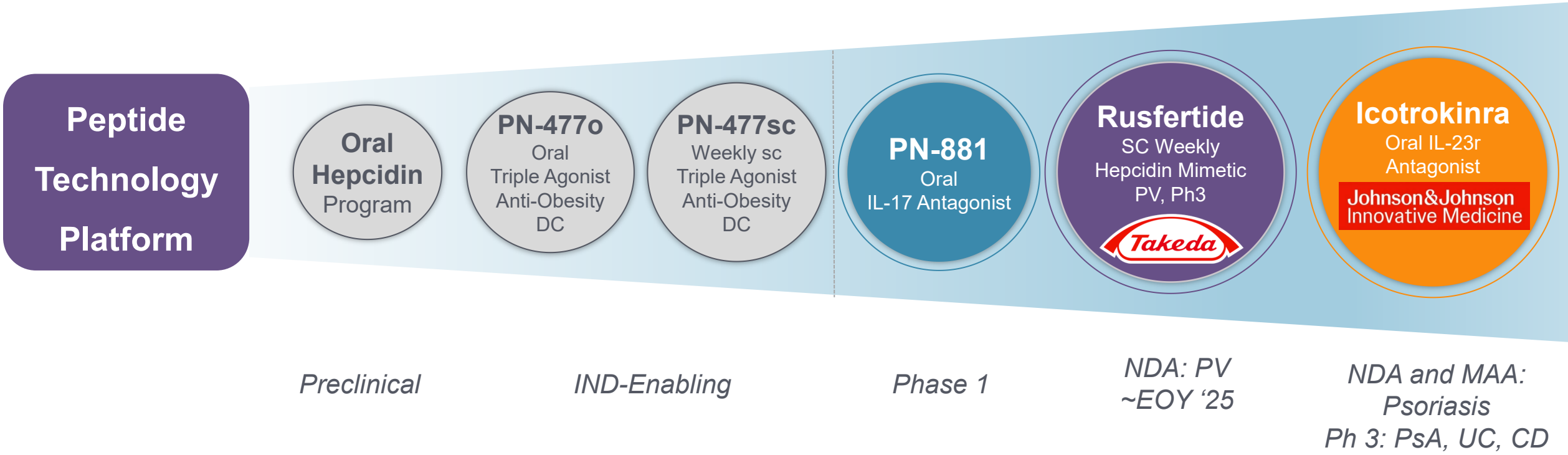
The forward-looking statements made in this presentation involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These forward-looking statements are subject to risks and uncertainties, including those discussed in Protagonist's 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 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. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation concerns products that are under clinical investigation and which have not yet been approved for marketing by the FDA. They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated. The trademarks included herein are the property of the owners thereof and are used for reference purposes only. Such use should not be construed as an endorsement of such products. Nothing contained in this presentation is, or should be construed as, a recommendation, promise or representation by the presenter or Protagonist or any director, employee, agent or advisor of Protagonist. This presentation does not purport to be all inclusive or to contain all the information you may desire.

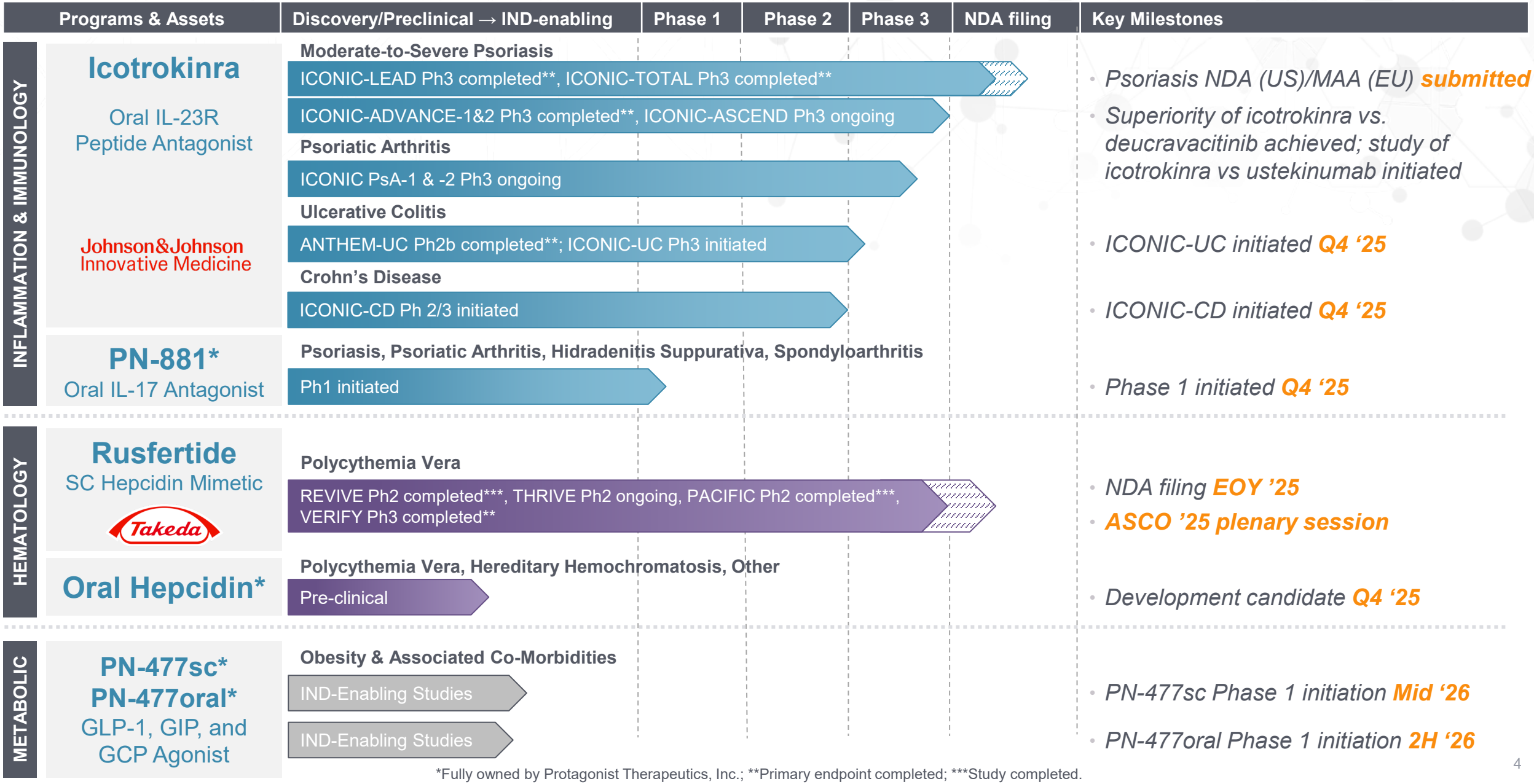
A Peptide Therapeutics Company

Protagonist Therapeutics

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



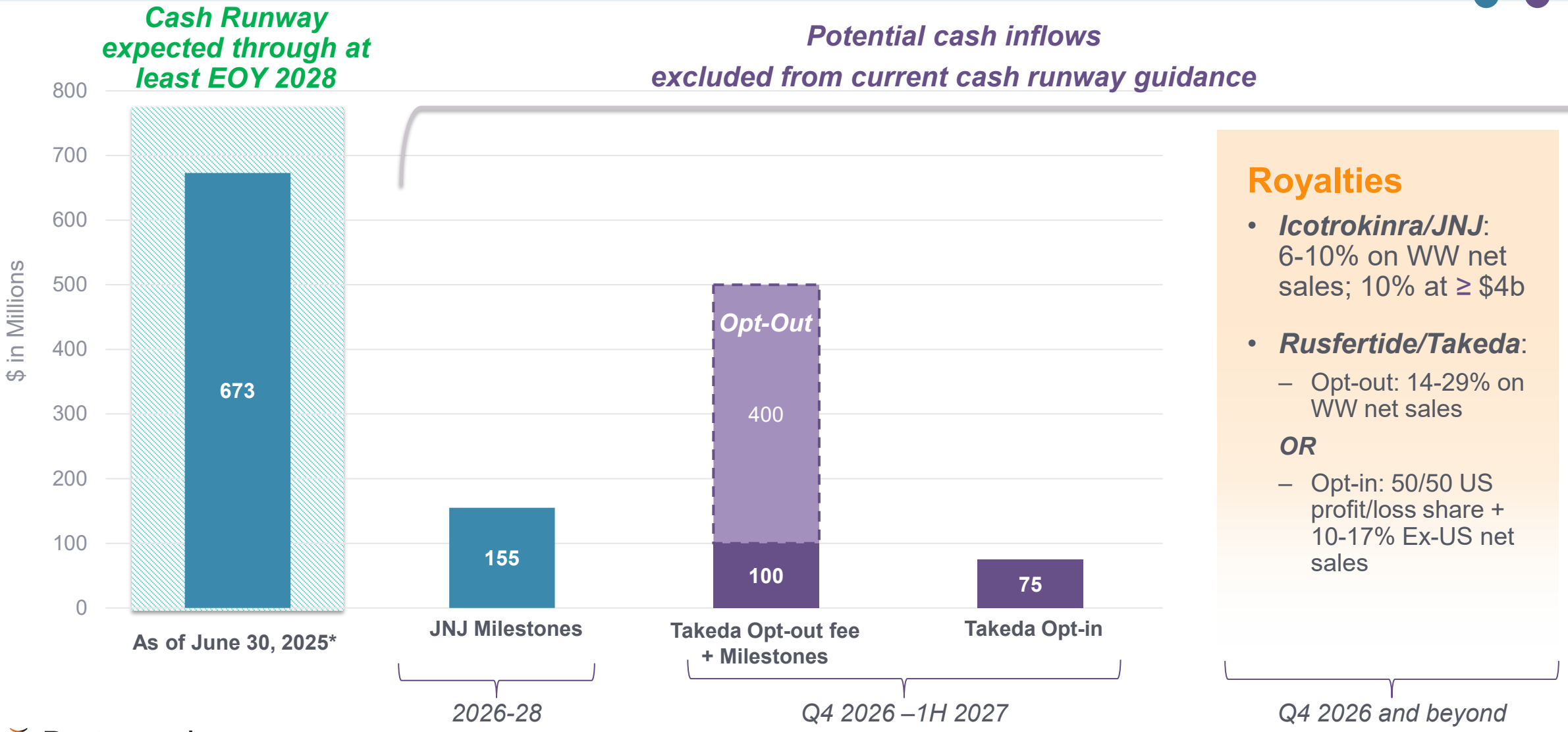
Pipeline of Proprietary and Partnered Programs



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

Protagonist On a Transformative Path Leading to Significant Potential Cash Inflows

2025-2028



Royalties

- ***Icotrokinra/JNJ***: 6-10% on WW net sales; 10% at ≥ $4b
- ***Rusfertide/Takeda***:
  - Opt-out: 14-29% on WW net sales

  OR
  - Opt-in: 50/50 US profit/loss share + 10-17% Ex-US net sales

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*represents total held in cash, cash equivalents and marketable securities as of June 30, 2025

Capital Allocation Considerations

- **R&D investments**
  - Develop internal programs up to clinical value inflection point
    - Oral IL-17 antagonist PN-881
    - Anti-obesity peptide(s)
    - Oral hepcidin mimetic/ferroportin blocker
    - New targets where peptides offer strong differentiation
  - Inorganic Growth
    - Opportunistic in-licensing/acquisition of technologies, programs, assets

- **Capital distribution**
  - Meaningful return of capital to shareholders at the right time
    - Share buy back program

Icotrokinra (JNJ-2113)

JNJ and Protagonist Collaboration

$337.5M
Upfront + milestones achieved to-date

$630M
future potential development and sales milestones

6% to 10% Royalty
10% at ≥ $4B net sales

Potential 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
	Total upcoming potential milestones	**$155M***	

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* $155M EXCLUDED from current cash runway forecast.

Rusfertide Co-Development and Co-Commercialization Partnership with Takeda

Takeda Partnership overview

- January 2024; $300M upfront received
- **Co-development**
  - Protagonist: Phase 3 completion and NDA filing
  - Takeda: Pre-commercial activities
- **Co-commercialization**
  - USA: 50:50 profit/loss share; commercial infrastructure not required for Protagonist
  - Ex-US: Takeda
- **Economics - Optionality**

Scenario	Total $$ upfront + milestones	Upfront	Payable Opt-Out	Potential Milestones	Royalty Rates	Comment
OPT-IN	$630M	$300M ✓	-	$330M	10-17% Ex-US	50:50 US profit/loss share
OPT-OUT	$1,675M	$300M ✓	$400M	$975M	14-29% worldwide	Exclusive US rights to Takeda

Potential 2025-26 Milestones

- **$25M** ✓
  Phase 3 VERIFY study 1° endpoint achievement
- **$75M** (opt-out) **or $50M** (opt-in) upon NDA approval

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Financial Highlights

Financial Resources Forecast Extends Through At Least Q4 2028

CASH, CASH EQUIVALENTS & MARKETABLE SECURITIES

$672.9M

as of
June 30, 2025

CASH RUNWAY FORECAST THROUGH AT LEAST

Q4 2028*

***Excludes** all near-term potential milestones from JNJ and Takeda

- **$155M in near-term - Icotrinkra**
- **$25M** Rusfertide
- **$50M** (or $75M if opted-out) Rusfertide NDA approval; and
- **Up to $400M, if** we exercise opt-out option

SHARES OUTSTANDING

~62.1M

as of
June 30, 2025

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Johnson&Johnson Innovative Medicine

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

Targeted Investigational Therapy for Psoriasis & Other IL-23 Mediated Diseases

Icotrokinra

First- and Only-in-Class ORAL IL-23 Receptor Antagonist in Clinical Development

JNJ Partnership overview

- 2017 to present: Icotrokinra
  - Protagonist completed pre-clinical and first Ph1 study
  - JNJ responsible for further development and commercialization
- **Successful outcome in four Phase 3 psoriasis studies**
  - **Psoriasis NDA submitted July 2025; EMA application submitted Sept 2025**
- **Successful outcome in Phase 2b ulcerative colitis study**
  - **Phase 3 in UC[1] initiated; Phase 2b/3 in Crohn's disease initiated[2]**
- Potential annual peak sales of Icotrokinra: $5B+[3,4]
  - Tremfya® annual peak sales projected at $10B+[5]
  - Skyrizi® annual peak sales projected at $20B+ by 2027[6]
  - Psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease

1. ClinicalTrials.gov. NCT07196748. Accessed on 1 October 2025; 2. ClinicalTrials.gov. NCT07196722. Accessed on 1 October 2025;
3. Stelara® generated $10.4B in sales; Tremfya® generated $3.7B in sales in 2024 (Johnson & Johnson Q4 earnings report). Stelara® and Tremfya® are not part of Protagonist-Janssen collaboration; 4. JNJ Innovative Medicines Enterprise Business Review, Dec 5, 2023; 5. JNJ Q2 earnings call, July 17, 2025;
6. Abbvie Full-year and Q4 2024 financial results, January 31, 2025.

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Icotrokinra Market Opportunity[1]

Blockbuster Potential for a Safe and Effective Oral, Once Daily Medication

Psoriasis/IBD patients eligible for advanced therapies, and yet aren't receiving them[2]

50-70%
(~5M)

Market growth is expected to be driven by orals[4]

75% Patients on injectables who would switch to an oral with similar safety & efficacy[3]

Combination of advanced efficacy and trusted safety in a preferred oral formulation could unlock a large market share

1. JNJ Innovative Medicines Enterprise Business Review, Dec 5th, 2023.
2. Global Quant Patient Opportunity Research – Jan 2022 (n=378)
3. Patient Oral v Inj Preference Research – Nov 2022 (n=395) – both in patients with moderate-to-severe plaque psoriasis
4. Clarivate and 2022 Epi Reports including internal assumptions
5. Evaluate Pharma WW Sales by Indication Sep 2023 extrapolated 2028-30

Protagonist Therapeutics

Icotrokinra Clinical Development Program

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

Plaque Psoriasis

FRONTIER 1 & 2 Ph2b, n = 255 & 227, in moderate-to-severe psoriasis	✓	Bissonnette R, et al. ***N Engl J Med.*** 2024;390:510-21.
ICONIC-LEAD Ph3, n = 684, in moderate-to-severe psoriasis	✓	Bissonnette R, et al. ***N Engl J Med.*** 2025;393:1784-95.
ICONIC-TOTAL Ph3, n = 311, psoriasis in special areas of body	✓	Gooderham M, et al. ***NEJM Evid.*** 2025;Epub ahead of print.
ICONIC-ADVANCE 1 Ph3, n = 774, Icotrokinra vs. Deucravacitinib	✓	Gold LS, et al. ***Lancet***. 2025;406:1363-74.
ICONIC-ADVANCE 2 Ph3, n = 731, Icotrokinra vs. Deucravacitinib	✓	
Pustular/Erythrodermic Psoriasis Ph3, n = 19	✓	
ICONIC-ASCEND Ph3, n = 675, Icotrokinra vs. Ustekinumab	Ongoing	

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

Psoriatic Arthritis

ICONIC-PsA 1 Ph3, n~540, in biologic-naive active psoriatic arthritis	Ongoing
ICONIC-PsA 2 Ph3, n~750, in biologic exposed active psoriatic arthritis	Ongoing

Ulcerative Colitis

ANTHEM-UC Ph2b, n ~252, in ulcerative colitis	✓
ICONIC-UC Ph3, n~882, in ulcerative colitis	New Study; recruiting

Crohn's Disease

ICONIC-CD Ph 2/3, n~1092, in Crohn's disease	New Study; recruiting

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Phase 3 ICONIC LEAD Study: Icotrokinra in Moderate-to-Severe PsO in Adults and Adolescents (N=684) Study Design

Key inclusion criteria:

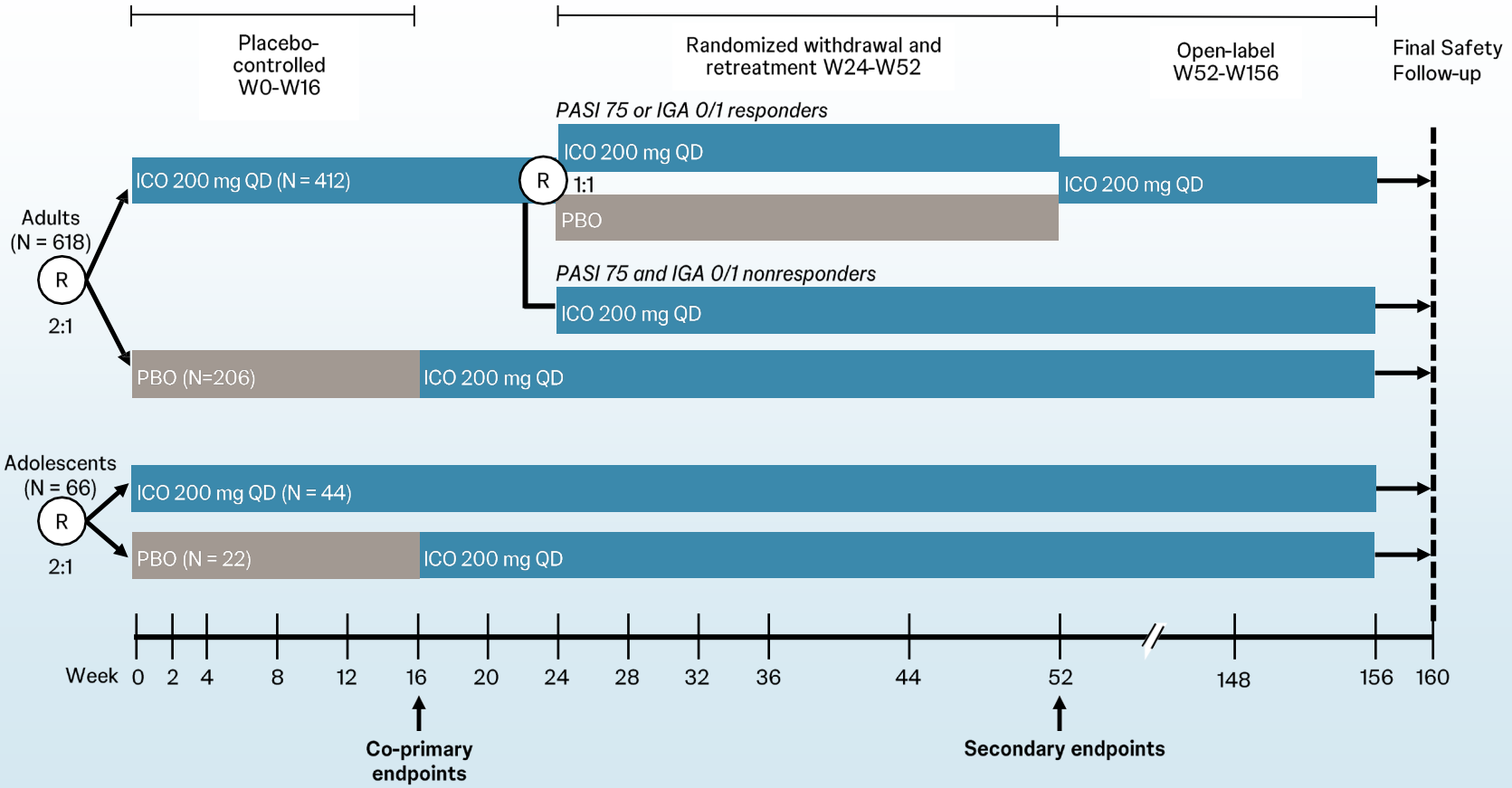
- ≥12 years
- Plaque PsO for ≥26 weeks
- Body surface area (BSA) ≥10%, Psoriasis Area and Severity Index (PASI) score ≥12, and Investigator's Global Assessment (IGA) score ≥3
- Candidate for phototherapy or systemic treatment for plaque PsO

Co-primary Endpoints:

- IGA 0/1 at Week 16
- PASI 90 at Week 16

Key secondary endpoints:

- Clinical outcomes (PASI 75/90/100, IGA 0) at Weeks 4, 8, and/or 16
- PROs (≥4-point improvement from baseline in PSSD Itch, PSSD Symptom 0) at Weeks 4, 8, and/or 16
- Scalp PsO (ss-IGA 0/1) at Week 16



Participants with the following intercurrent events were considered as nonresponders: discontinued study drug due to a lack of efficacy or AE of worsening PsO or initiated prohibited medication that could impact PsO. After accounting for these intercurrent events, nonresponder imputation was applied to participants with missing data.

AE, adverse event; IGA 0/1, IGA score of 0 (clear)/1 (almost-clear) and a ≥2-grade improvement; PASI 75/90/100, reduction from baseline of 75%/90%/100% in the PASI score; PBO, placebo; PSSD, Psoriasis Symptom and Sign Diary; QD, once daily; R, randomization; ss-IGA, scalp-specific Investigator's Global Assessment; ss-IGA 0/1, ss-IGA score of 0 (clear)/1 (almost clear) and a ≥2-grade improvement from baseline.

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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: Randomized Treatment Withdrawal in Adults (Weeks 24-52) and Continuous ICO Treatment in Adolescents (Through Week 52)[1,2]

ICO Demonstrated Superior Maintenance of Skin Response Among Adult Week 24 ICO Responders

- Icotrokinra demonstrated superior maintenance of skin response among adult Week 24 responders and robust and durable skin clearance rates in adolescents through Week 52

	Adults (≥18 years old)[1,2]					
	Proportion of Participants					
	Week 24	Week 52	Week 24	Week 52	Week 24	Week 52
ICONIC-LEAD	**IGA 0/1[a]**		**PASI 90[a]**		**PASI 75[a]**	
ICO→PBO at Week 24	100	23	100	21	100	30
ICO→ICO at Week 24 200 mg QD	100	82	100	84	100	89
	Adolescents (≥12 years to <18 years old)[1,2]					
	Week 24	**Week 52**	**Week 24**	**Week 52**	**Week 24**	**Week 52**
ICONIC-LEAD	**IGA 0/1[b]**		**PASI 90[b]**		**PASI 75[b]**	
PBO→ICO at Week 16	82	91	50	77	NA	91
ICO 200 mg QD	86	82	89	86	NA	95

[a]Among Week 24 ICO IGA 0/1, PASI 90, and PASI 75 responders, respectively. [b]Proportion of participants.
IGA, Investigator's Global Assessment; IGA 0/1, IGA score 0/1 & ≥2-grade improvement from baseline; ICO, icotrokinra; NA, not available; PASI, Psoriasis Area and Severity Index; PBO, placebo; QD, once-daily.

Protagonist Therapeutics

1. Presented at the European Academy of Dermatology and Venerology Meeting, September 17-20, 2025, Paris, France. 2. Presented at the 2025 SDPA 23rd Annual Fall Dermatology Conference; November 5-9, 2025; San Antonio, TX, USA.

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

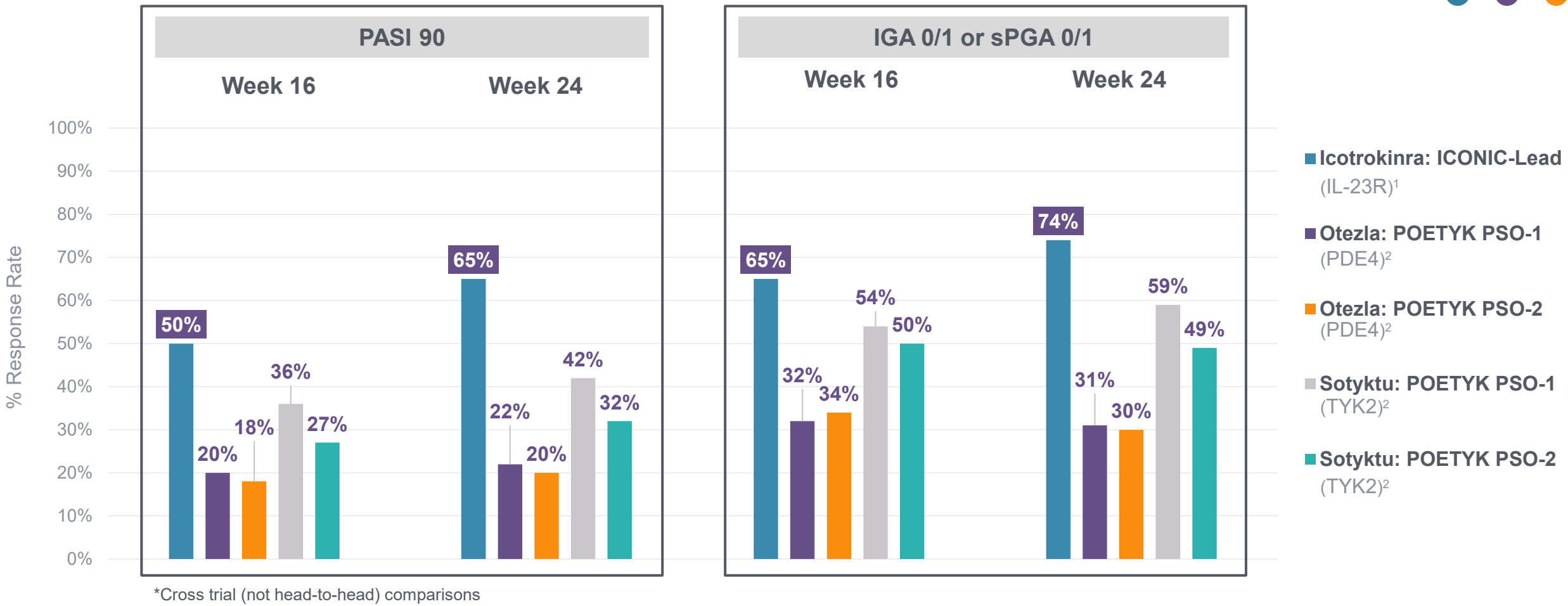
Safety analysis set included all randomized and treated participants. [a]Includes data after Week 16 for PBO-randomized participants who crossed over to receive ICO. [b]Combined withdrawal and retreatment group. [c]Based on gastrointestinal disorders SOC. [d]Included adenocarcinoma of colon and prostate 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.

Icotrokinra in ICONIC-LEAD vs Oral Approved Phase 3 Benchmarks*

Best-in-Class Oral Psoriasis Targeted Therapy Potential



*Cross trial (not head-to-head) comparisons

1. Johnson & Johnson. "Icotrokinra delivered an industry-leading combination of significant skin clearance with demonstrated tolerability in a once daily pill in Phase 3 topline results." News release. 18 November 2024.
2. Sotyktu [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. [https://packageinserts.bms.com/pi/pi_sotyktu.pdf] September 2022. Accessed on 15 November 2024.

Phase 3 ICONIC-TOTAL: Plaque PsO and Difficult-to-Treat High Impact Sites (N=311) Study Design[1,2]

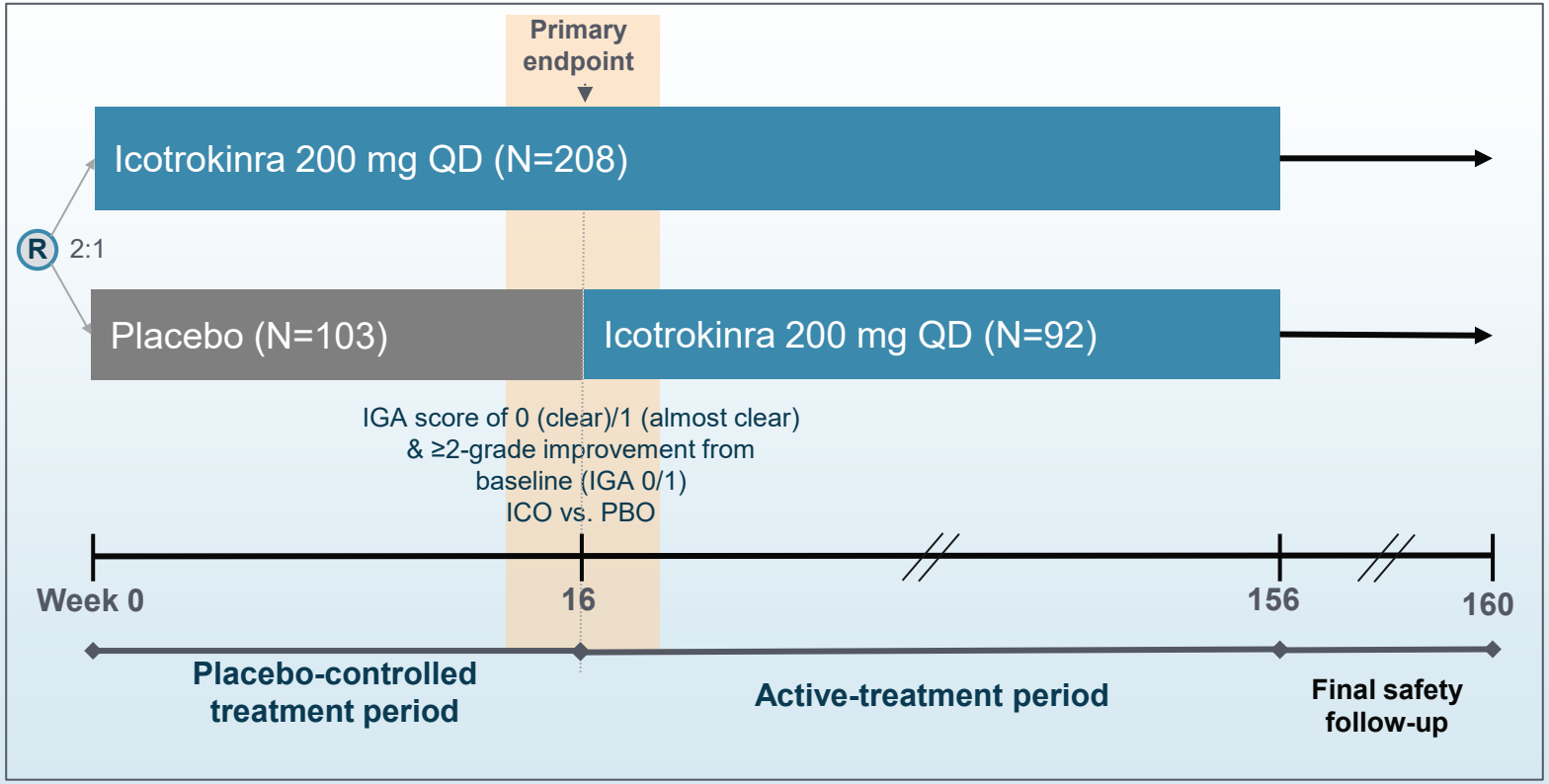
Adults & adolescents with plaque PsO involving high-impact sites evaluated using a basket-like study design

Key inclusion criteria:

- ≥12 years old
- Plaque PsO for ≥26 weeks
- BSA ≥1% AND IGA score ≥2
- At least moderate high-impact PsO involving ≥1 site:
  - **Scalp PsO:** ss-IGA score ≥3
  - **Genital PsO:** sPGA-G score ≥3
  - **Hand/foot PsO:** hf-PGA-G score ≥3
- Candidate for phototherapy or systemic treatment for plaque PsO and failed ≥1 topical

Primary endpoint:

- ICO vs. PBO: IGA score of 0 (clear)/1 (almost clear) & ≥2-grade improvement from baseline (IGA 0/1)



BSA, body surface area; ICO, icotrokinra; IGA, Investigator's Global Assessment; PBO, placebo; PsO, psoriasis; R, randomization.

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.

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.

ICONIC-TOTAL: Plaque PsO and Difficult-to-Treat High Impact Sites[1]

Week 52 Efficacy and Safety Summary

- Icotrokinra demonstrated high and durable rates of PsO clearance, including clear/almost clear or completely clear rates for scalp PsO, genital PsO, and hand/foot PsO at week 52
- Icotrokinra provided substantial mean improvement (62%) in nail PsO at week 52
- AE profile of icotrokinra was similar to placebo through week 16, with stable exposure-adjusted incidence rates through week 52
  - No icotrokinra safety signal was identified through week 52

	Week 52								
			Scalp		Genital		Hand/Foot		Nail
ICONIC-TOTAL	**IGA 0/1**	**IGA 0**	**ss-IGA 0/1[a]**	**ss-IGA 0[a]**	**sPGA-G 0/1[a]**	**sPGA-G 0[a]**	**Hf-PGA 0/1[a]**	**Hf-PGA 0[a]**	**mNAPSI[a]**
PBO→ICO	68	45	71	61	94	86	68	58	59
Icotrokinra 200 mg QD	67	44	72	57	85	73	62	58	62

All values in the table represent percentages unless stated otherwise.
AE, adverse event; 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; mNAPSI, modified Nail Psoriasis Severity Index; PBO, placebo; PsO, plaque psoriasis; QD, once daily; R, Randomization; sPGA-G, static Physician's Global Assessment of Genitalia; ss-IGA, scalp-specific Investigator's Global Assessment.

Protagonist Therapeutics

1. Presented at the Fall Clinical Dermatology Conference; October 23-26, 2025; Las Vegas, NV, USA.

Phase 3 ICONIC TOTAL Study: Exposure-adjusted AE rates were consistent across groups and study phases[1]

ICO AE Profile Similar to PBO Through Week 16; No ICO Safety Signal Identified Through Week 52

	PBO-Controlled (Week 0–16)		Week 16–52	Through Week 52	
	ICO (N=208)	PBO (N=103)	PBO→ICO (N=92)	ICO (N=208)	ICO Combined (N=300)
Mean Weeks / Total PY of Follow-Up	16.0 / 63.6	15.6 / 30.8	36.2 / 63.9	49.3 / 196.4	45.3 / 260.2
Any AE	105 (50%)	46 (45%)	51 (55%)	153 (74%)	204 (68%)
Incidence/100PY (95% CI)[b]	233 (188, 277)	217 (154, 280)	132 (96, 168)	169 (142, 195)	158 (136, 179)
SAE	1 (<1%)	2 (2%)	1 (1%)	6 (3%)	7 (2%)
Incidence/100PY (95% CI)[b]	2 (0, 5)	7 (0, 16)	2 (0, 5)	3 (1, 6)	3 (1, 5)
AE Leading to D/C	6 (3%)	4 (4%)	0 (0%)	7 (3%)	7 (2%)
Incidence/100PY (95% CI)[c]	10 (4, 21)	13 (4, 34)	0 (0, 5)	4 (1, 7)	3 (1, 6)
Infection	59 (28%)	23 (22%)	39 (42%)	106 (51%)	145 (48%)
Incidence/100PY (95% CI)[b]	110 (82, 138)	88 (52, 124)	81 (56, 106)	81 (66, 96)	81 (68, 94)
Serious Infection	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Incidence/100PY (95% CI)[c]	0 (0, 5)	3 (<1, 18)	0 (0, 5)	0 (0, 2)	0 (0, 1)
GI AE	15 (7%)	8 (8%)	7 (8%)	21 (10%)	28 (9%)
Incidence/100PY (95% CI)[b]	25 (12, 37)	27 (8, 46)	11 (3, 20)	12 (7, 17)	12 (7, 16)
Malignancy[d]	1 (<1%)	0 (0%)	0 (0%)	2 (1%)	2 (1%)
Incidence/100PY (95% CI)[c]	2 (<1, 9)	0 (0, 10)	0 (0, 5)	1 (<1, 4)	1 (<1, 3)

Data shown are n (%) unless otherwise noted. [a]Includes data for ICO-randomized patients through Week 52 and for PBO-to-ICO patients from Week 16 through Week 52. [b]CIs were based on a Wald statistic using the normal assumption. [c]CIs were based on an exact method assuming that the observed number of events follows a Poisson distribution. [d]Includes chronic lymphocytic leukemia and malignant melanoma in situ. D/C, discontinuation; GI, gastrointestinal; SAE, serious AE.

Protagonist Therapeutics

1. Presented at the Fall Clinical Dermatology Conference; October 23-26, 2025; Las Vegas, NV, USA.

ICONIC-ADVANCE 1 and 2: Study Design

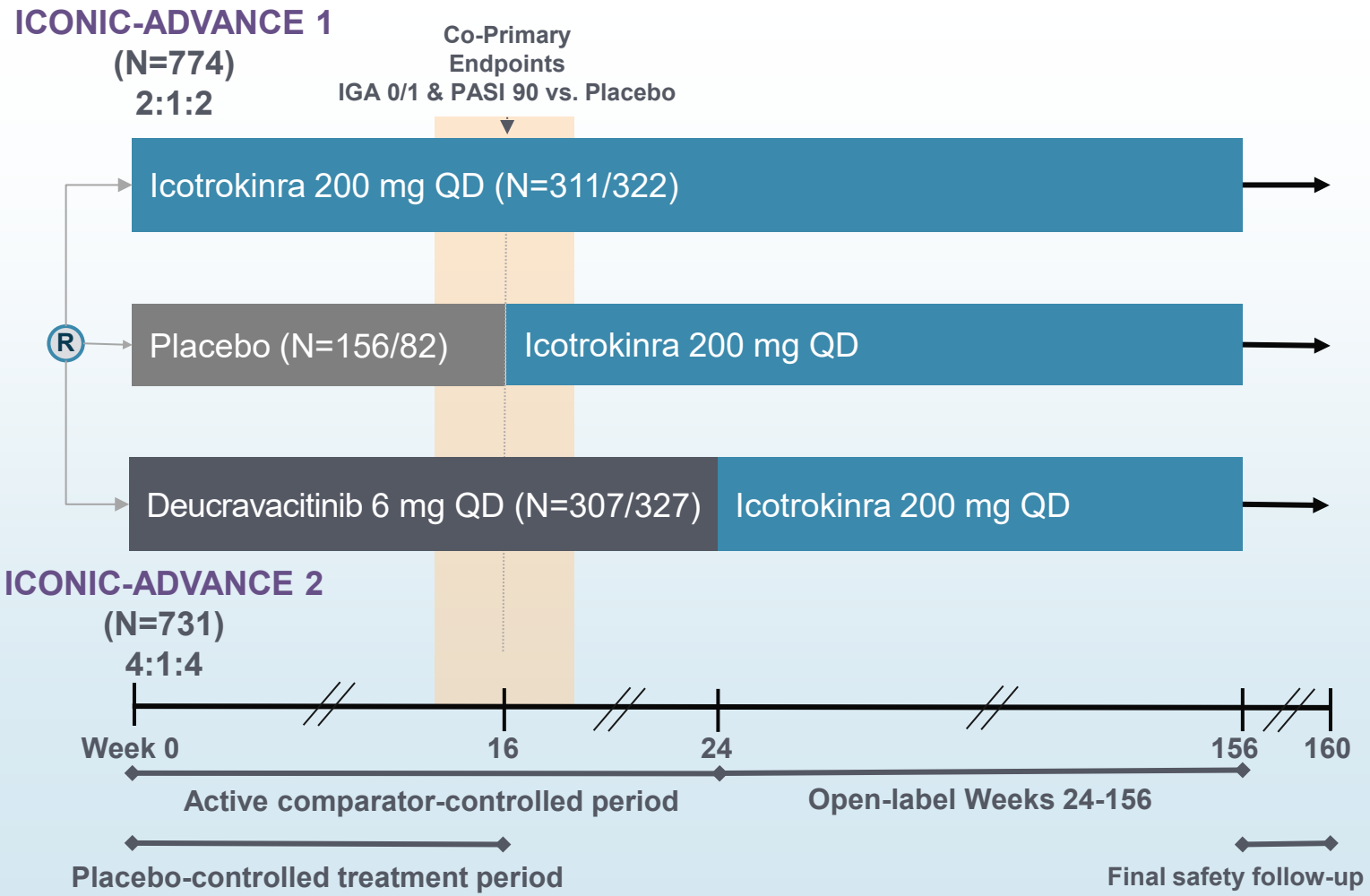
Moderate-to-severe Plaque PsO

Key inclusion criteria

- ≥18 years
- Plaque PsO for ≥26 weeks
- BSA ≥10%; PASI score ≥12; IGA score ≥3
- Candidate for phototherapy or systemic treatment for plaque PsO
- Suitable candidate for Deucra per approved product labeling

Co-primary endpoints

- IGA score 0/1 & ≥2-grade improvement from baseline (IGA 0/1) vs PBO at Week 16
- PASI 90 vs PBO at Week 16



BSA, body surface area; Deucra, deucravacitinib; ICO, icotrokinra; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PBO, placebo; PsO, psoriasis; QD, once daily; R, randomization.

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.

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

Week 24 Efficacy Summary: Co-Primary and Key Secondary Endpoints

	Week 24							
	IGA 0/1		PASI 90		IGA 0		PASI 100	
ICONIC-ADVANCE	**-1**	**-2**	**-1**	**-2**	**-1**	**-2**	**-1**	**-2**
Icotrokinra 200 mg QD	74 **(Δ+22)**	68 **(Δ+13)**	66 **(Δ+25)**	65 **(Δ+22)**	48 **(Δ+27)**	40 **(Δ+19)**	41 **(Δ+25)**	33 **(Δ+17)**
Deucra 6 mg QD	52	55	41	43	21	21	16	16

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. **Purple** numbers in parentheses show the difference between icotrokinra and deucravacitinib for each stated endpoint.

- In the pivotal phase 3 ICONIC-ADVANCE 1 & 2 studies, adults with moderate-to-severe plaque PsO receiving icotrokinra demonstrated superior skin clearance and symptom relief vs deucravacitinib at Week 24
  - At Week 16, placebo patients crossed over to receive icotrokinra
  - All endpoints improved numerically from Week 16 to Week 24 in the placebo group

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: AE Profile Similar to Placebo Through Week 16[1,2]

Overall AE Rates Through Week 24 Were Lower With Icotrokinra Than Deucra

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
Any AE	136 (57%)	303 (48%)	360 (57%)	359 (57%)	411 (65%)
Incidence/100 PY (95% CI)[b]	314 (254, 361)	225 (200, 251)	300 (268, 330)	201 (180, 221)	263 (237, 288)
Serious AE	4 (2%)	14 (2%)	14 (2%)	18 (3%)	20 (3%)
Incidence/100 PY (95% CI)[b]	6 (<1, 9)	7 (3, 11)	7 (4, 11)	6 (3, 9)	7 (4, 10)
Serious infection[c]	1 (<1%)	1 (<1%)	4 (1%)	3 (<1%)	4 (1%)
Incidence/100 PY (95% CI)[b]	1 (0, 9)	1 (0, 3)	2 (1, 6)	1 (<1, 3)	1 (<1, 4)
Malignancy[d]	1 (<1%)	3 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
Incidence/100 PY (95% CI)[b]	1 (0, 9)	2 (<1, 5)	1 (0, 3)	1 (<1, 3)	1 (<1, 3)
AE leading to discontinuation	12 (5%)	13 (2%)	14 (2%)	15 (2%)	17 (3%)
Incidence/100 PY (95% CI)[b]	17 (6, 24)	7 (3, 10)	7 (4, 11)	5 (3, 8)	6 (3, 9)

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]Incidence/100 PY: number of pts with AEs/total PY at risk × 100; CI based on study-size adjusted Wald statistics. cIncluded arthritis bacterial in the PBO group, infective exacerbation of chronic obstructive airways disease and pneumonia in the ICO group, and campylobacter colitis, lower respiratory tract infection, viral infection, and viral upper respiratory tract infection in the Deucra group. dIncluded invasive ductal breast carcinoma in the PBO group, pancreatic carcinoma and hepatic metastases, breast cancer, and keratoacanthoma in the ICO group, and buccal squamous cell carcinoma and malignant melanoma in situ in the Deucra group; all considered unrelated to study treatment by investigators. AE, adverse event; CI, confidence interval; Deucra, deucravacitinib; ICO, icotrokinra; PBO, placebo; PY, participant-years; 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.

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.

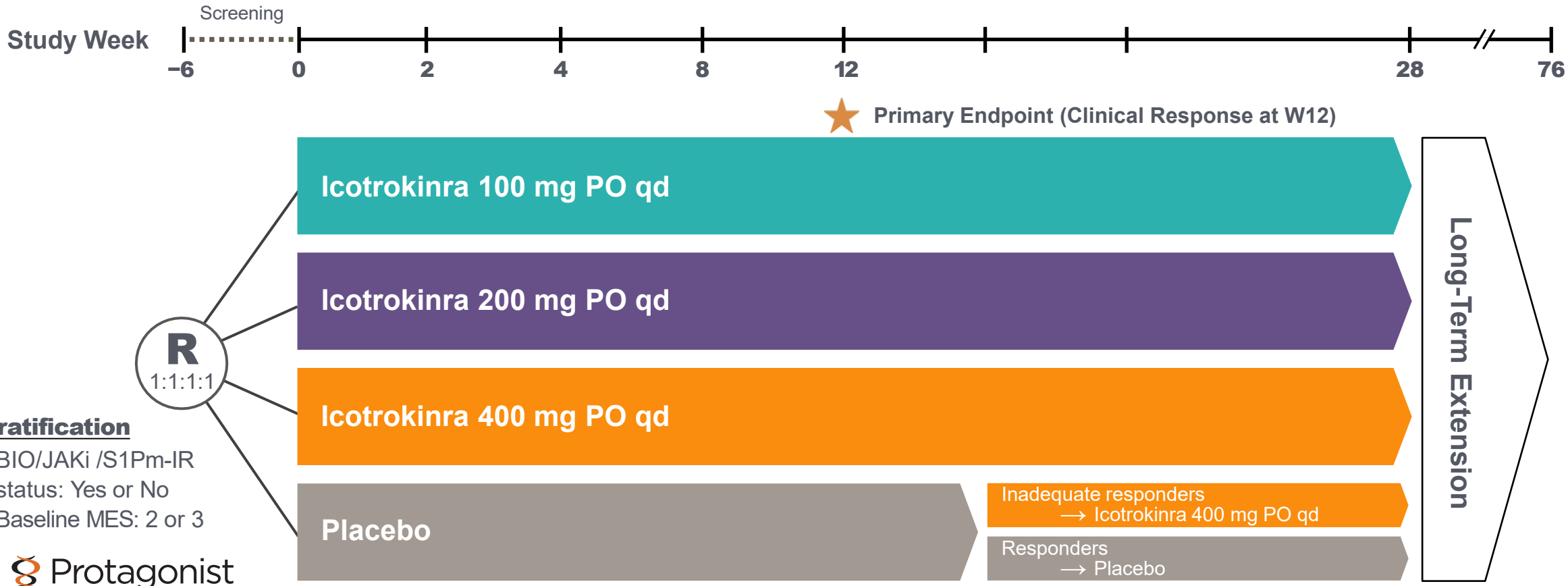
Protagonist Therapeutics

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.

ANTHEM-UC Study Design

Key Eligibility Criteria

- Diagnosed UC of ≥12 weeks duration and a modified Mayo score (mMS) of 5–9, inclusive
- Mayo endoscopic subscore (MES) ≥2 per central review of screening video endoscopy
- Inadequate response/intolerance (IR) to corticosteroids, 6-MP, or AZA **OR** corticosteroid dependence **OR** IR to TNFα antagonists, ustekinumab, vedolizumab, JAK inhibitors, or S1P modulators (BIO/JAKi /S1Pm-IR)



Stratification

- BIO/JAKi /S1Pm-IR status: Yes or No
- Baseline MES: 2 or 3

Protagonist Therapeutics

Phase 2b ANTHEM-UC Study[1,2]

Week 12 and 28 Efficacy Summary: Primary and Secondary Endpoints

- Icotrokinra (400 mg QD) demonstrated sustained and clinically meaningful results at weeks 12 and 28 compared with placebo

	Week 12[1,2]				Week 28[2]			
Regimen	**Clinical Response***	**Clinical Remission**	**Symptomatic Remission**	**Endoscopic Improvement**	**Clinical Response**	**Clinical Remission**	**Symptomatic Remission**	**Endoscopic Improvement**
Placebo	27.0	11.1	19.0	14.3	25.4	9.5	20.6	11.1
100 mg QD	54.7 **(Δ+27.7)**	21.9 **(Δ+10.9)**	53.1 **(Δ+34.1)**	26.6 **(Δ+12.4)**	60.9 **(Δ+35.8)**	40.6 **(Δ+31.2)**	51.6 **(Δ+31.1)**	50.0 **(Δ+39.2)**
200 mg QD	58.1 **(Δ+30.8)**	24.2 **(Δ+13.0)**	41.9 **(Δ+22.7)**	33.9 **(Δ+19.7)**	62.9 **(Δ+37.5)**	33.9 **(Δ+24.4)**	53.2 **(Δ+32.6)**	38.7 **(Δ+27.7)**
400 mg QD	63.5 **(Δ+36.3)**	30.2 **(Δ+19.2)**	46.0 **(Δ+26.9)**	36.5 **(Δ+22.4)**	66.7 **(Δ+41.3)**	31.7 **(Δ+22.4)**	52.4 **(Δ+32.0)**	38.1 **(Δ+27.2)**

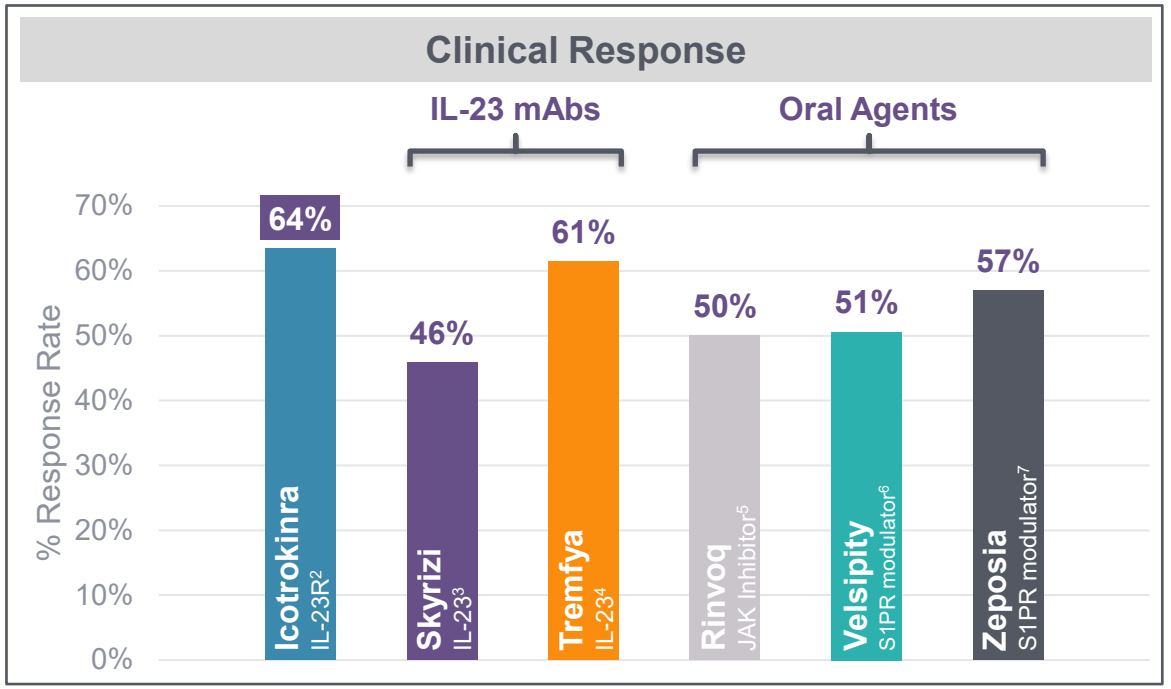
*Primary endpoint.
All values represent percentages. Numbers in parentheses show the difference between icotrokinra and placebo at a specified dose for each stated endpoint.

Protagonist Therapeutics

1. Presented at the United European Gastroenterology Week, October 4-7, 2025, Berlin, Germany; 2. Presented at the American College of Gastroenterology, October 24-29, 2025, Phoenix, AZ.

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

Clinical Response



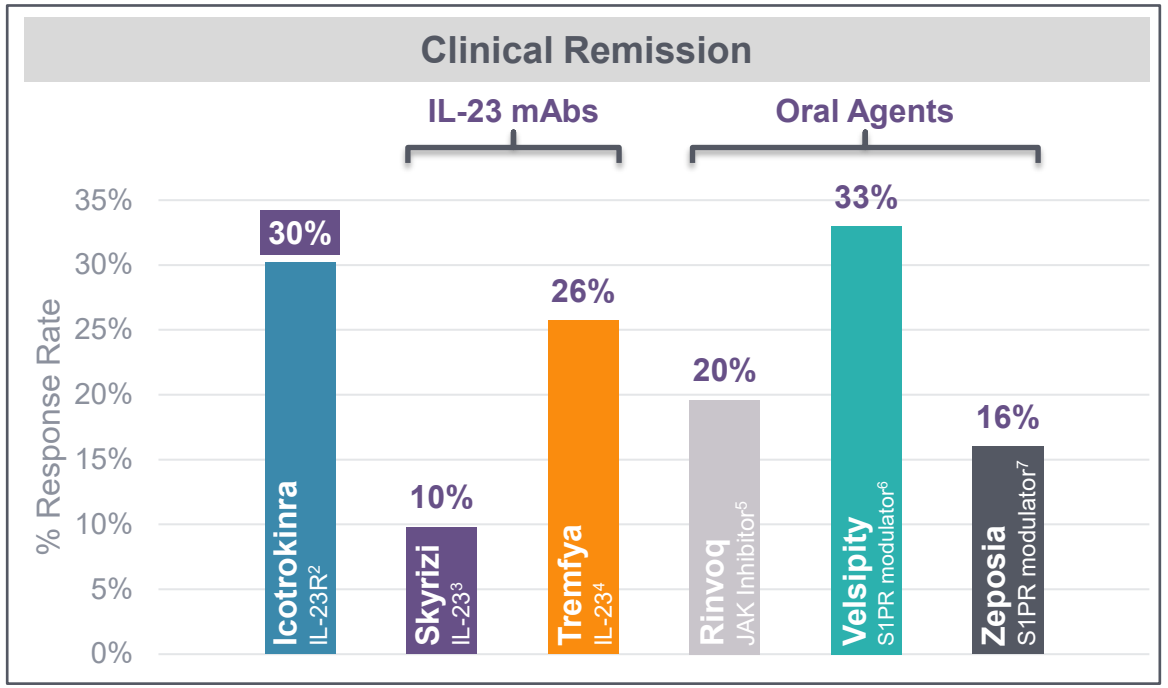
Agent	Endpoint Timeframe	Placebo Response (%)
Icotrokinra	Wk 12	27.0
Skyrizi	Wk 12	20.0
Tremfya	Wk 12	27.6
Rinvoq	Wk 8	13
Velsipity	Wk 12	32.5
Zeposia	Wk 8	37

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 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

ANTHEM-UC: Proportions of Participants Experiencing AEs Were Similar for PBO and All ICO Doses Through Week 28[1]

Icotrokinra Was Well Tolerated in Study Participants

	Placebo[a]	Icotrokinra 100 mg qd	Icotrokinra 200 mg qd	Icotrokinra 400 mg qd	Combined icotrokinra[b]
Safety analysis set, N	63	64	62	63	189
Average duration of follow-up, weeks	20.3	26.6	26.1	26.0	26.2
Average duration of treatment, weeks	19.5	25.4	25.1	25.2	25.2
Deaths, n (%)	0	0	0	0	0
Participants with 1 or more, n (%)					
AEs	39 (61.9%)	42 (65.6%)	41 (66.1%)	38 (60.3%)	121 (64.0%)
Serious AEs	6 (9.5%)	0	3 (4.8%)	1 (1.6%)	4 (2.1%)
AEs leading to discontinuation of study agent	7 (11.1%)	0	4 (6.5%)	2 (3.2%)	6 (3.2%)
Infections[c]	17 (27.0%)	18 (28.1%)	24 (38.7%)	15 (23.8%)	57 (30.2%)
Serious infections[c]	1 (1.6%)	0	0	0	0
Most common AEs, n (%)					
Worsening of ulcerative colitis	8 (12.7%)	4 (6.3%)	9 (14.5%)	5 (7.9%)	18 (9.5%)
Upper respiratory tract infection	1 (1.6%)	8 (12.5%)	4 (6.5%)	6 (9.5%)	18 (9.5%)
Nasopharyngitis	4 (6.3%)	5 (7.8%)	4 (6.5%)	6 (9.5%)	15 (7.9%)
Headache	1 (1.6%)	6 (9.4%)	3 (4.8%)	4 (6.3%)	13 (6.9%)

a. Includes data for all placebo group participants while receiving placebo.
b. Includes data for all participants randomized to icotrokinra.
c. Infections were defined as any adverse event coded to the MedDRA system organ class 'Infections and infestations'.

Protagonist Therapeutics

1. Presented at the American College of Gastroenterology, October 24-29, 2025, Phoenix, AZ.

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.

Icotrokinra Summary

NDA Seeking FDA Approval for Plaque Psoriasis Submitted July 2025; MAA Submitted September 2025

Psoriasis (PsO)

- 4 Phase 3 ICONIC trials in moderate-to-severe plaque psoriasis (PsO)
  - Approximately 65% of patients achieve PASI 90 and approximately 75% of patients achieve IGA 0/1 by Week 24
  - Nearly 50% of patients had completely clear skin (IGA 0) at Week 24
  - Icotrokinra showed superiority vs. deucravacitinib at Weeks 16 and 24 in the proportions of patients achieving PASI 75, 90, 100, IGA 0/1, and IGA 0, as well as no symptoms as measured by PSSD 0
  - Phase 3 ICONIC-TOTAL results in pts with plaque PsO and difficult-to-treat, high-impact site involvement extend results from the ongoing phase 3 ICONIC-LEAD study evaluating icotrokinra in adults & adolescents with moderate-to-severe plaque PsO
- A phase 3 study (ICONIC-ASCEND) of icotrokinra vs. the injectable biologic Stelara is underway

Psoriatic Arthritis (PsA)

- 2 Phase 3 trials in moderate-to-severe PsA have been initiated: ICONIC-PsA 1 in bio-naïve patients and ICONIC-PsA 2 in bio-experienced patients

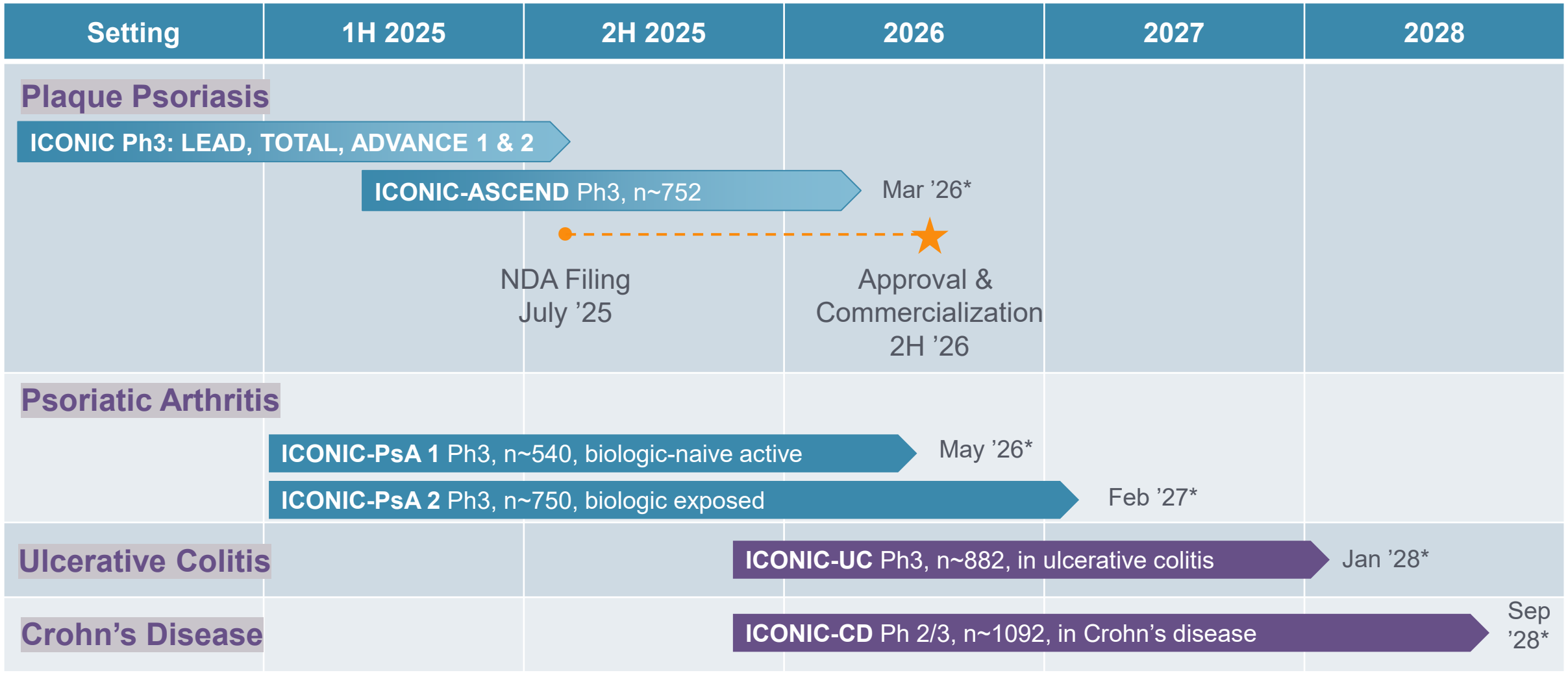
Ulcerative Colitis (UC)

- Phase 2b ANTHEM-UC study in patients with moderately to severely active UC: Icotrokinra met the primary endpoint of clinical response in all dose groups
  - Clinical response rates of up to 63.5% and clinical remission rates up to 30.2% at week 12 and a favorable safety profile observed in the phase 2b ANTHEM UC study
  - Clinical response and remission rates continued to improve through Week 28
- ICONIC-UC Phase 3 study initiated

Crohn's Disease (CD)

- ICONIC-CD phase 2/3 study initiated

Icotrokinra: Clinical Development, Approval and Commercialization Timelines



Protagonist Therapeutics

* Primary Completion Date

Protagonist Therapeutics

Takeda

Rusfertide
A Synthetic Mimetic of the Natural Hormone Hepcidin

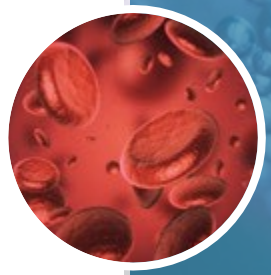
Addressing Unmet Needs in Polycythemia Vera

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.

Protagonist Therapeutics

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.

Protagonist Therapeutics

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

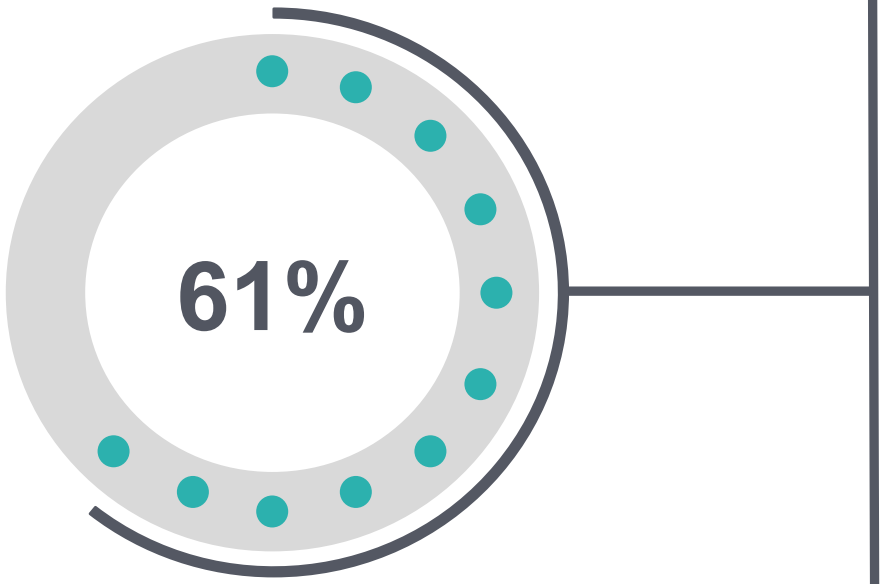
Occurrence of thrombotic events following treatment initiation can be an indicator of the ineffectiveness of the treatment – an example of a sub-optimally controlled PV patient

Protagonist Therapeutics

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.

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.

Rusfertide Launch Readiness

Market Insights
Generate key market insights to inform commercial strategy, data generation and payer evidence

Clinical Value
Rapid, consistent and durable Hct control + symptom relief, which fulfills a significant unmet need and benefits patients

Scientific Exchange
Data generation, medical communications, awareness of unmet need in PV, MSLs, advisory boards

Ensure Access
Market access strategy which navigates dynamic payer landscape and is aligned with clinical value and supported by clinical evidence

Scale For Success
Customer engagement model which supports patient needs and maximizes the opportunity for rusfertide

Protagonist Therapeutics

Patient Journey in PV Identifies Unmet Need in Current Treatment Paradigm

Patients Cycle Through Treatment Options with Inconsistent Hct and Tolerability

Presentation and Diagnosis

Initial presentation: Routine blood work or thrombotic event

Work Up: Blood tests prompt a referral to Hematology/Oncologist

Diagnosis: Hem/Onc diagnoses PV, JAK-2 genetic testing and assesses risk

Initial Treatment and Management

Immediate: Phlebotomy (PHL) after diagnosis

- **LOW RISK: Regular PHL** to reduce Hct
  - PHL inconsistently, temporarily reduces Hct
  - PHL results in iron deficiency; amplifies PV symptoms
- **HIGH RISK: PHL with HU or Interferon** if PHL alone is insufficient

"I don't love phlebotomy. Most patients hate it. It's exchanging PV for symptomatic iron deficiency…nobody can sustain that."

- MPN Specialist

Cycling Through Treatment Options

- **Introduces 2L/3L treatments** if not controlled and/or patient QoL is not manageable
- **2L HU** an off-label[1] cytoreductive chemotherapy
- **Ruxolitinib or ropeginterferon** added for Hct control or tolerability and/or based on HCP preference

Current 2L+ therapies may have side effects and *safety* concerns

*"There's **side effects that make HU impossible to take for some patients**… 30% of patients drop off."*

- MPN Specialist

Ongoing PV Management

Monitor blood counts and treatment side effects

Adjusts treatment as necessary

HCPs also educate patients on lifestyle modifications, symptom surveillance, and treatment adherence through the management of PV

*Recommended threshold levels for hematocrit = 45% in men and 42% in women

1. HU is an off-label treatment in the US

Polycythemia Vera (PV)

Rusfertide Clinical Development Program

- 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
Polycythemia Vera (PV)				
VERIFY Ph 3, n=293				• Topline 32-Wk Primary EP results ✓
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 in OLE
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** for PV

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

Protagonist Therapeutics

Rusfertide Phase 3 **VERIFY** Study

Clinical Study Design and Topline Results

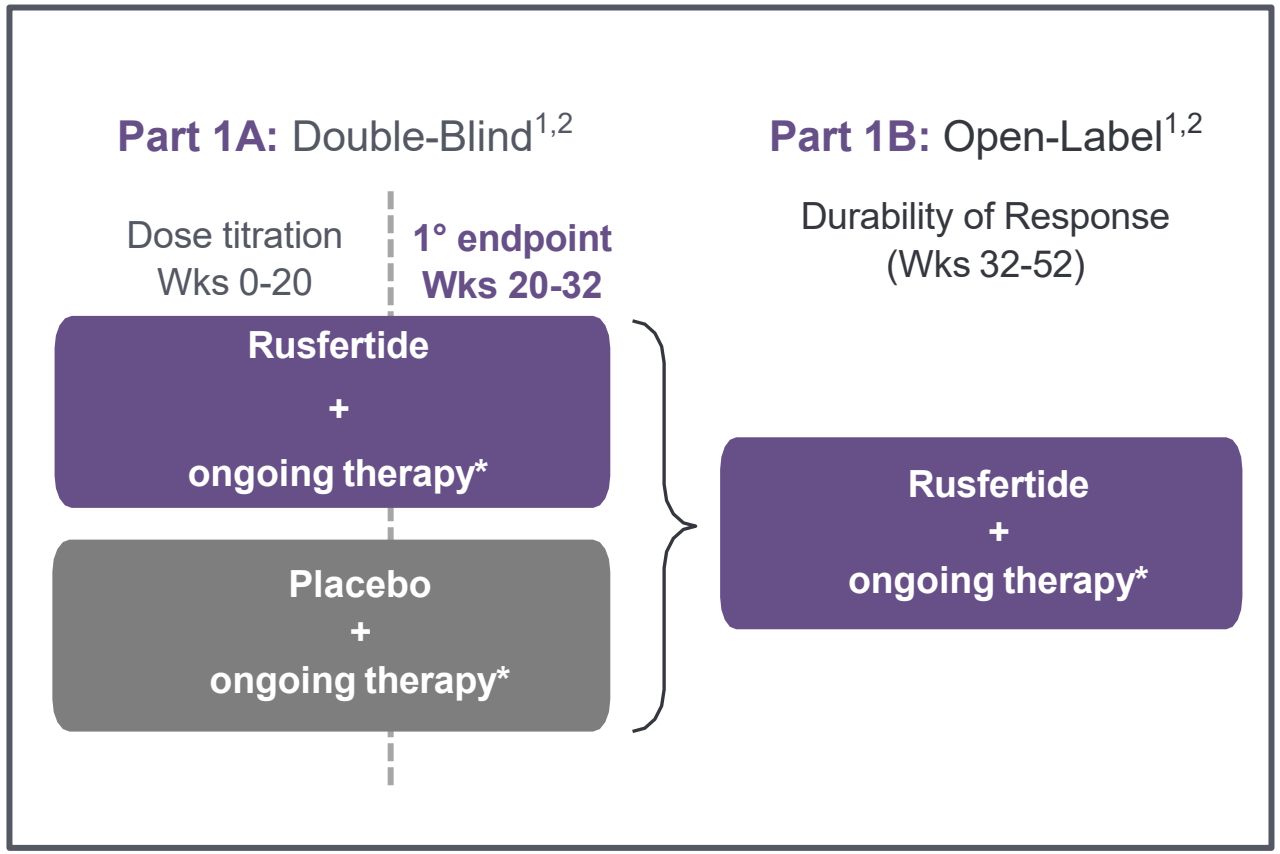
ASCO 2025 Plenary Session

Inclusion Criteria

≥3 PHL (28 wks prior)
OR
≥5 PHL (1 year prior)

N = 293

1:1 randomization



Primary endpoint:[3] Wks 20-32

1. **Clinical Response: rusfertide vs placebo (p<0.0001)** ✓

Key 2° endpoints: Wks 0-32

1. **Average number of PHLs[4] (p<0.0001)** ✓
2. **Proportion of patients with Hct <45% (p<0.0001)** ✓
3. **Average PROMIS Fatigue SF-8a Score[5]** ✓
4. **Average MFSAF Total Symptom Score[6]** ✓

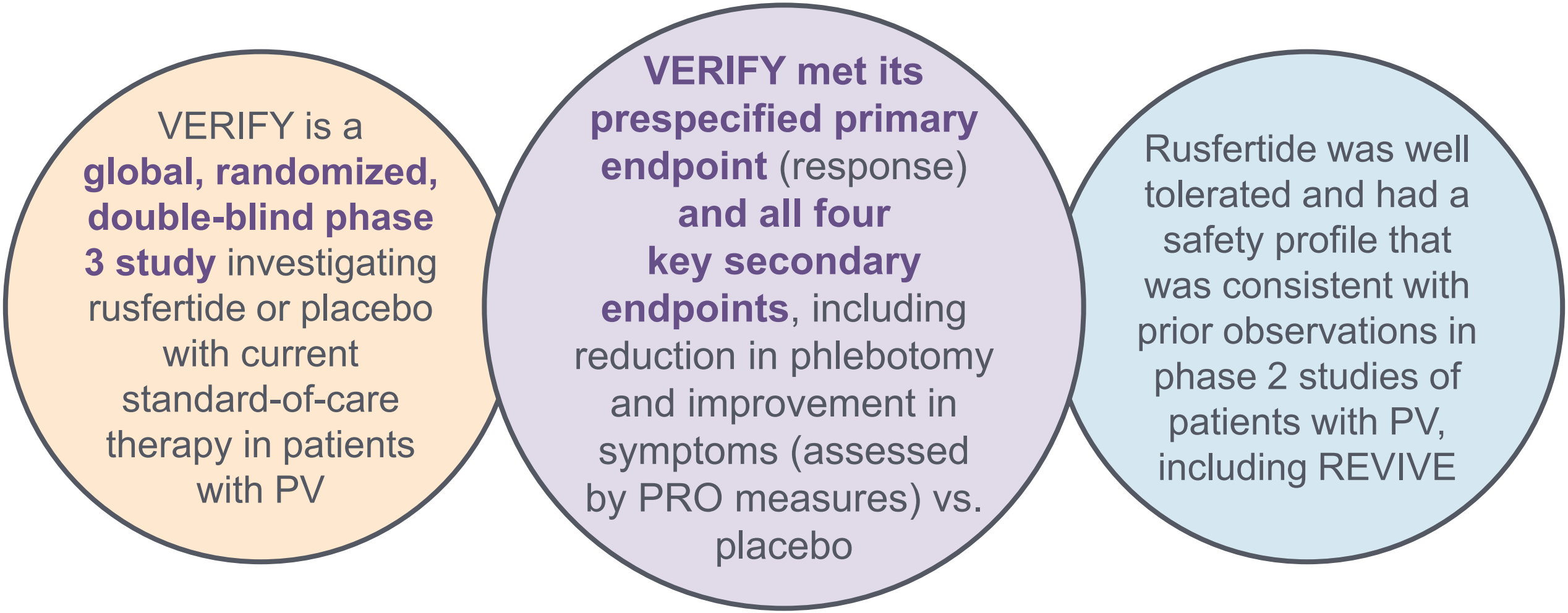
*Ongoing therapy could include therapeutic phlebotomy and/or cytoreductive therapy.

1. ClinicalTrials.gov. NCT05210790. https://clinicaltrials.gov/ct2/show/NCT05210790;
2. ASCO'24: Bankar A, et al. VERIFY: A randomized controlled phase 3 study of the hepcidin mimetic rusfertide (PTG-300) in patients with polycythemia vera (PV). J Clin Oncol;2024;42;16_suppl. TPS6592.
3. US primary endpoint
4. EU primary endpoint
5. Garcia SF, et al. *J Clin Oncol*. 2007;25:5106-12; Cella D, et al. *J Clin Epidemiol*. 2016;73:128-34
6. Mesa RA, et al. *Leuk Res*. 2009;33:1199-203; Gwaltney C, et al. *Leuk Res*. 2017;59:26-31

Protagonist Therapeutics

Key Takeaway Points from Phase 3 VERIFY Study in Polycythemia Vera (PV)[1]

Link to Phase 3 VERIFY Study Results Presentation Available Here



Protagonist Therapeutics

1. Plenary presentation at American Society of Clinical Oncology (ASCO) by Dr. Andrew T. Kuykendall, MD, June 01, 2025; Chicago, IL, USA.

Rusfertide for Polycythemia Vera

Successful Completion of Phase 2 and 3 Studies

- Phase 2 **REVIVE** Study (N=70):
  - Randomized withdrawal data presented at EHA 2023[1] (late-breaking oral presentation); data published in *NEJM*[2]
  - Long-term extension data presented at ASH 2023[3] and EHA 2024;[4] final data presented at ASH 2024[5]
    - Full Analysis Population: 69.2% responder rate (vs. 14.8% placebo; p<0.0001)[5]
    - Randomized Analysis Population: 60% responder rate (vs. 13.8% placebo; p=0.0004)[5]
- Phase 2 **THRIVE** Study (N=46):
  - Long-term extension study (for REVIVE patients on study years 3-5)
- Phase 2 **PACIFIC** Study (N=20)[6]:
  - High hematocrit (Hct >48%); 52-week open-label study completed in Q2 2023
- Phase 3 **VERIFY** Study (N=293)[7,8]
  - Primary endpoint and all four key secondary endpoints achieved in March 2025
  - Data presented in oral plenary presentation at ASCO'25[9] and will be included in regulatory filings (eg, NDA, MAA)

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

Protagonist Therapeutics

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. Ginzburg Y, et al. *Blood*. 2023;142 (Supplement 1): 3208. 7. Verstovsek S, et al. *Blood* 2022; 140 (Supplement 1): 3929–3931. 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. Results from VERIFY, a phase 3, double-blind, placebo (PBO)-controlled study of rusfertide for treatment of polycythemia vera (PV). *J Clin Oncol.* 2025;43(17_suppl):LBA3.

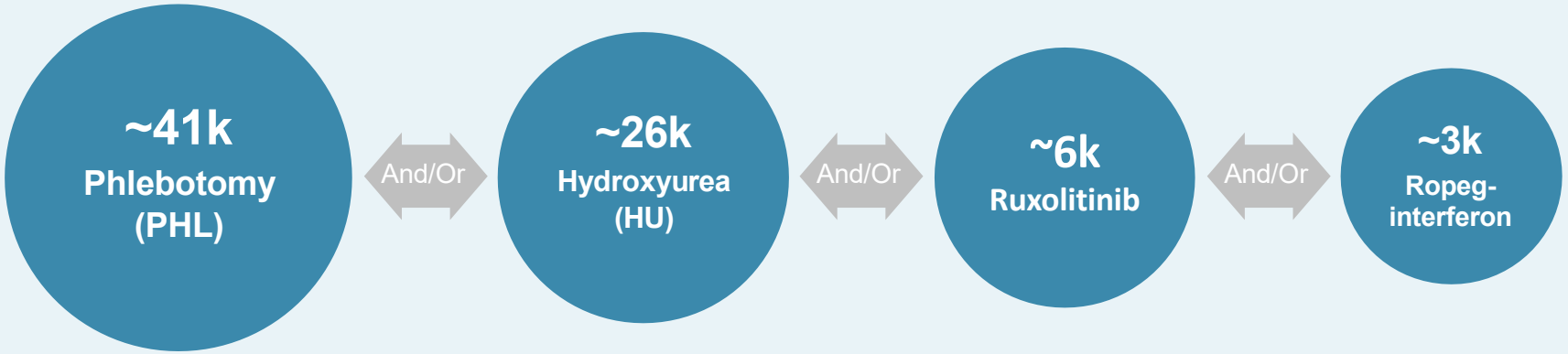
Polycythemia Vera: Prevalence, Treatment Paradigm and Unmet Need

Uncontrolled Hematocrit Exists at Each Step of Treatment

~155k diagnosed patients in the US with **~78k treated**[2]

Treatment Paradigm

Patients are often on polytherapy and will cycle through various treatments[2]



- Unmet need exists at each step of the treatment landscape
  - **~78% with uncontrolled Hct<45%**[3]
- **Rusfertide expected to be used at each step**[1]

Rusfertide may provide consistent hematocrit control and reduce treatment burden to achieve peak revenue potential of $1-2B

1. Takeda R&D Day, December 2024
2. Komodo Health closed claims dataset (2016-2023); Note: ~2,000 patients are treated via a combination of other therapies
3. 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

Protagonist Therapeutics

67th ASH Annual Meeting and Exposition (Orlando, FL; 6-9 December 2025)

Four Protagonist-Sponsored Oral/Poster Presentations Focusing on Rusfertide

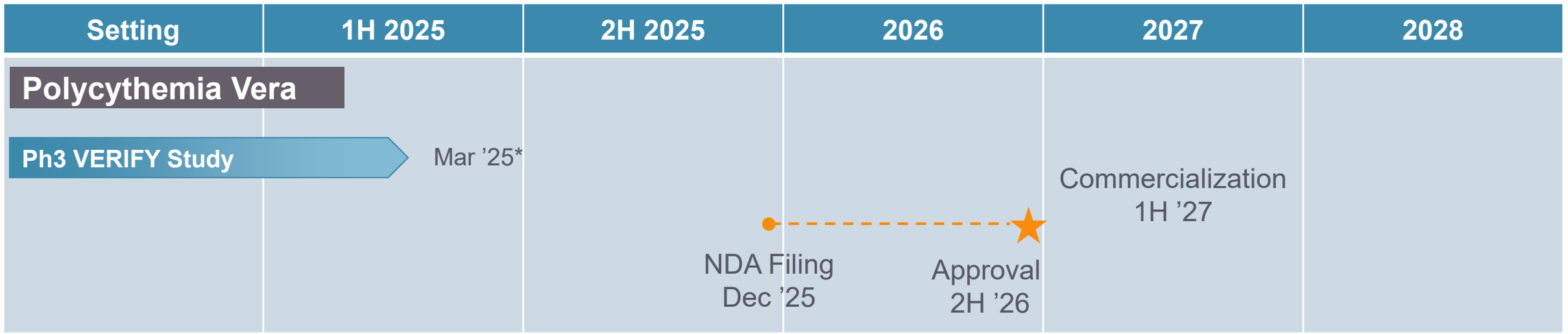
- **Phase 3 VERIFY Study 52-Week Data Oral Presentation**
  - **Title:** Rusfertide or placebo plus current standard-of-care therapy for polycythemia vera: Durability of response and safety results through week 52 from the randomized controlled phase 3 VERIFY study
  - **Presenter:** Andrew T. Kuykendall (Moffitt Cancer Center)
  - **Session Name:** 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Expanding the Therapeutic and Prognostic Landscape in Myeloproliferative Neoplasms, Mastocytosis and Hypereosinophilic Syndrome
  - **Date and Time:** December 6, 2025; 10:00-10:15 am EST
  - **Room:** OCCC - W414CD

- **Phase 2 THRIVE Study Poster Presentation**
  - **Title:** Long-term rusfertide treatment in polycythemia vera: Initial results from the phase 2 THRIVE extension study
  - **Presenter:** Naveen Pemmaraju (MD Anderson Cancer Center)
  - **Session Name:** 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Poster II
  - **Date and Time:** December 7, 2025; 6:00-8:00 pm EST
  - **Room:** OCCC - West Halls B3-B4

- **Phase 3 VERIFY Study PRO Poster Presentation**
  - **Title:** Comprehensive analyses of patient-reported outcomes from the phase 3 VERIFY study of rusfertide or placebo plus current standard of care for polycythemia vera
  - **Presenter:** Aniket Bankar (Princess Margaret Cancer Centre)
  - **Session Name:** 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Poster III
  - **Date and time:** December 8, 2025; 6:00-8:00 pm EST
  - **Room:** OCCC - West Halls B3-B4

- **Phase 3 VERIFY Study Dermatologic Screening Data Poster Presentation**
  - **Title:** Should dermatologic examinations become routine standard of care in patients with polycythemia vera? Observations from the phase 3 VERIFY study prior to rusfertide exposure
  - **Presenter:** Joseph Shatzel (Oregon Health & Sciences University)
  - **Session Name:** 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Poster III
  - **Date and Time:** December 8, 2025; 6:00-8:00 pm EST
  - **Room:** OCCC - West Halls B3-B4

Rusfertide for PV: Clinical Development, Approval and Commercialization Timelines



* Primary Completion Date

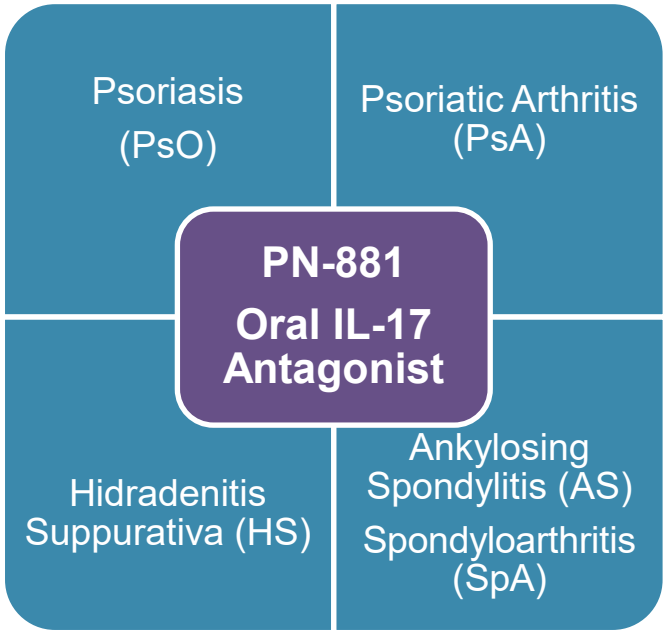
Protagonist Therapeutics

PN-881: Oral Peptide IL-17 Antagonist Development Candidate

PN-881: Oral IL-17 Peptide Antagonist Program

Best-in-Class Oral IL-17 Antagonist Potential

- IL-17: Clinically & commercially validated target[1]:
  - Cosentyx®, Taltz®, Bimzelx®
  - Expected to capture 31% of the PsO market by 2031, generating $9.3B
  - Growth from PsA, HS, and AS/SpA → additional sales of $7.7B by 2034
- **PN-881:** Differentiated target product profile (TPP)
  - **Potential for best-in-class oral peptide IL-17 antagonist[2]**
  - Specificity for IL-17A and IL-17F ligands (IL-17 AA, AF & FF)[3]
- Next Steps
  - Phase 1 SAD/MAD[4] study initiation ~Q4 2025
  - Phase 1 results → phase 2 psoriasis study
  - Rapid expansion into other IL-17-mediated diseases



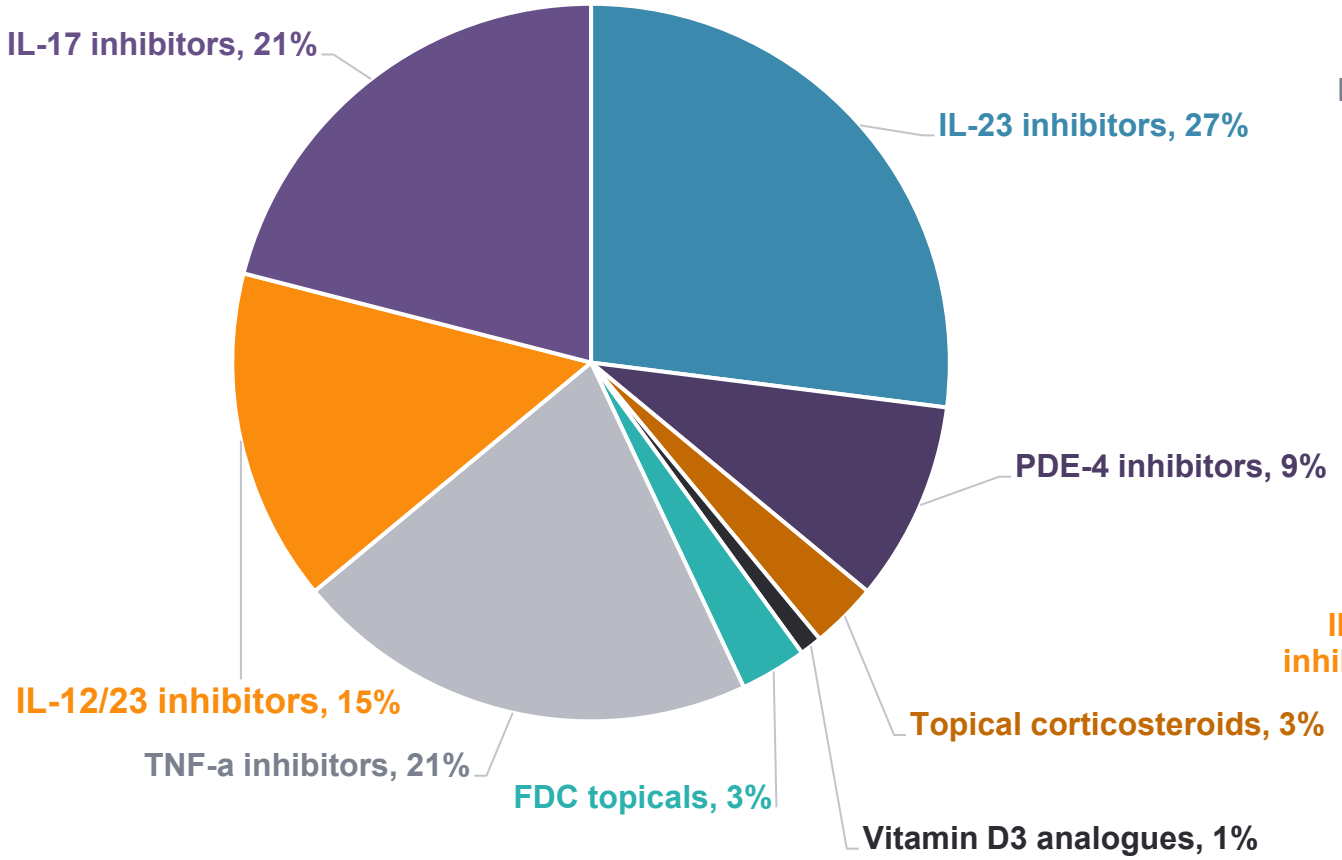
1. Psoriasis Disease Landscape and Forecast (Clarivate, 2023);
2. No approved oral IL-17 antagonists. Approved IL-17 mAbs: COSENTYX (secukinumab), TALTZ (ixekizumab), and BIMZELX (bimekizumab)
3. Blockade of both IL-17A and IL-17F leads to greater efficacy. Reich et al., N Engl J Med 2021;385:142-52. DOI: 10.1056/NEJMoa2102383
4. SAD = single ascending dose, MAD = multiple ascending dose

Protagonist Therapeutics

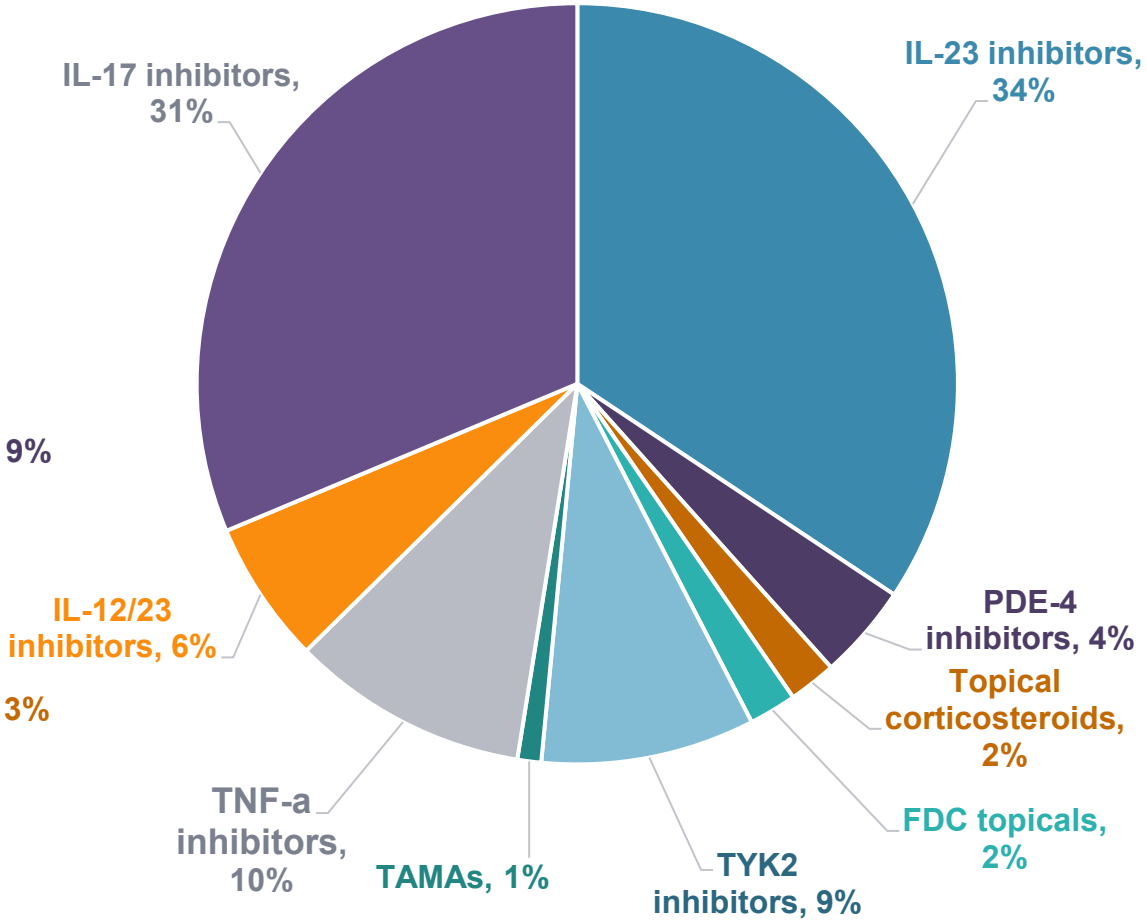
Psoriasis Market Share by Drug Class

IL-17 and IL-23 Inhibitors Expected to Dominate Market Share

2021 DISTRIBUTION
Market Size: $21.7B



2031 DISTRIBUTION
Market Size: $30.1B

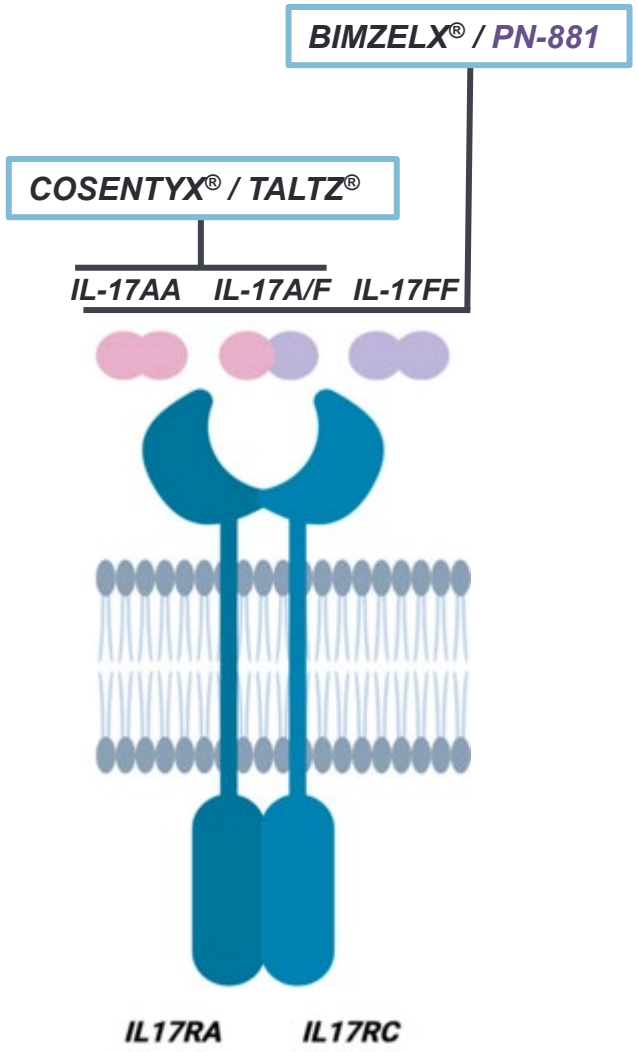


Protagonist Therapeutics

Psoriasis Disease Landscape and Forecast (Clarivate, 2023).

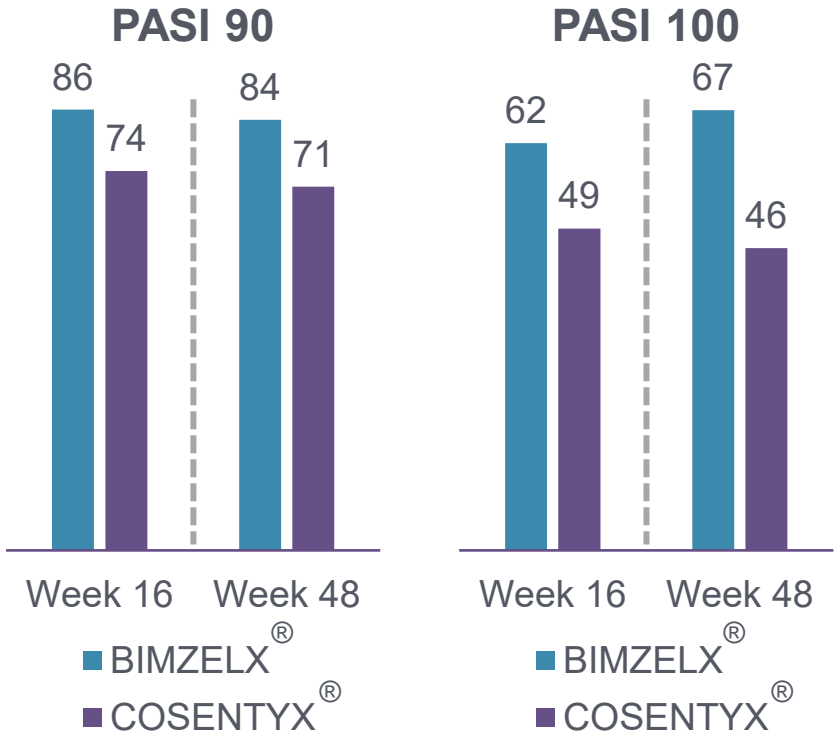
IL-17 Receptor Activated by Three Dimeric Forms of IL-17: IL-17AA, AF, and FF[1]

Oral PN-881 Designed to Inhibit IL-17AA, AF, and FF



BE RADIANT Clinical Trial:

Blockade of IL-17A and F Yields Greater Efficacy in Psoriasis[1]



Protagonist Therapeutics

[1]Reich et al., *N Engl J Med*. 2021;385:142-52.

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

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

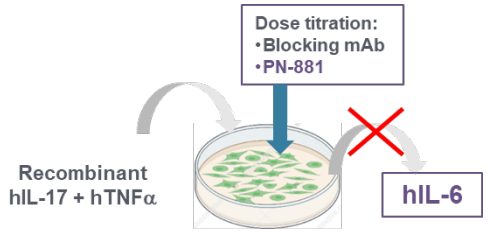
Attribute	Criteria
Potency	• **Sub-nM potency *vs.* IL-17 AA** • **Blocks all dimeric forms of IL-17: AA, AF, FF**
Stability	• Stable in simulated gastric and intestinal fluids • Stable in serum with $t_{1/2}$ >24 hr • Metabolic stability • Thermostability
PK	• Oral exposure and half-life in rodent and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

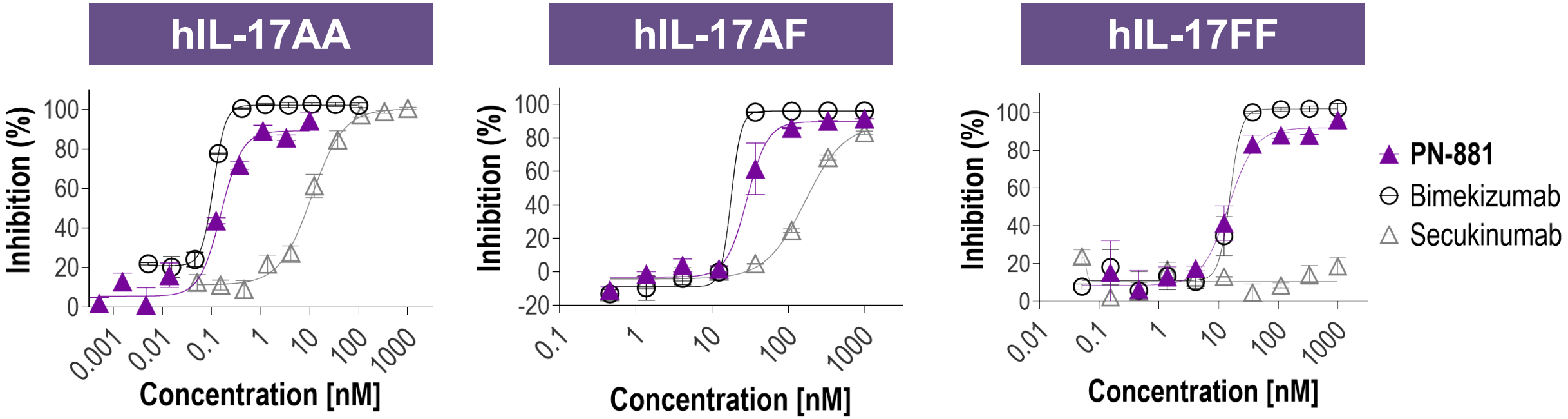
Protagonist Therapeutics

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

PN-881 Inhibits IL-17-induced IL-6 Responses With Similar Potency as Bimekizumab in Primary Human Dermal Fibroblast (HDFn) Assay[1]

- **PN-881** has similar blocking curves as **bimekizumab** for all three IL-17 isoforms while **secukinumab's** curves for IL-17AA and AF are shifted to the right
- Secukinumab does not block IL-17FF





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 and IL-17FF[1]

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

PN-881 vs Competitors	Neonatal Human Dermal Fibroblast (nHDF) and Human HT-1080 Fibrosarcoma Cell Line (HT-1080) IC_{50}s (nM)					
	IL-17 AA		IL-17 AF		IL-17 FF	
	nHDF	HT-1080	nHDF	HT-1080	nHDF	HT-1080
Oral Agents						
PN-881	**0.15**	**0.13**	**29**	**27**	**15**	**14**
DC-806[2] (or close analogue)	109	228	ND	ND	Inactive	Inactive
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.
2. Compound #166 from DICE patent: US 2020/0247785 A1. DC-806 development discontinued & replaced with DC-111.

- **PN-881** has sub-nM IL-17AA blocking potency (IC_{50}) similar to **bimekizumab** (Bimzelx®) and 70 times more potent than **secukinumab** (Cosentyx®)
- **PN-881** inhibited IL-17 AF and FF with similar potency to **bimekizumab** (Bimzelx®)

Protagonist Therapeutics

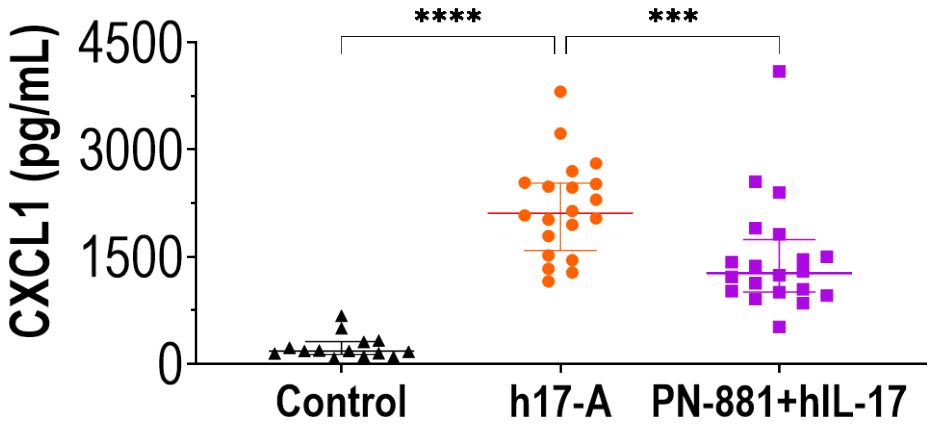
Oral PN-881 Neutralizes Human IL-17 in Mouse IL-17 Challenge PD Model[1]

PN-881 Significantly Reduces Serum and Skin CXCL1 Levels After Oral Administration

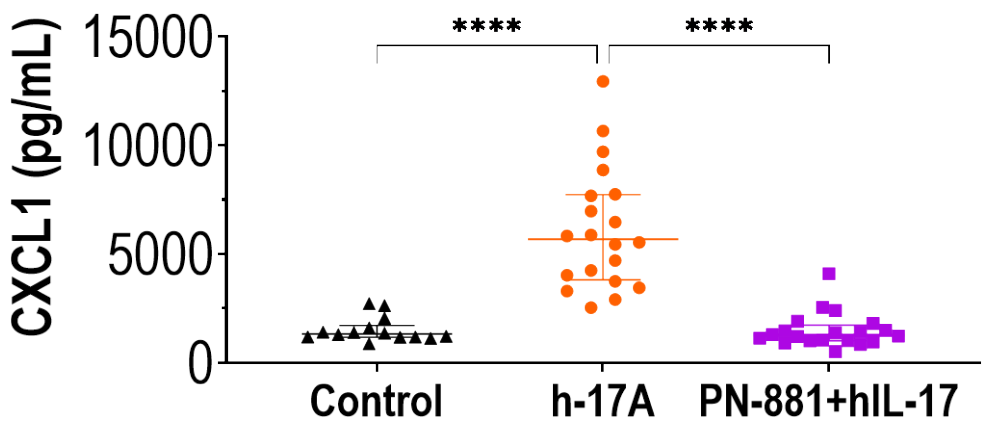
Treatment Groups:
a) Vehicle control
b) IL-17 alone
c) PN-881 (PO, QD)

1 hr → rhIL-17AA (SC 2µg/Mouse) or vehicle administered → 2 hr → Serum or skin collected → **CXCL1 (ELISA)**

Serum



Skin



***p<0.001, ****p<0.0001 dop plot depict median and interquartile ranges

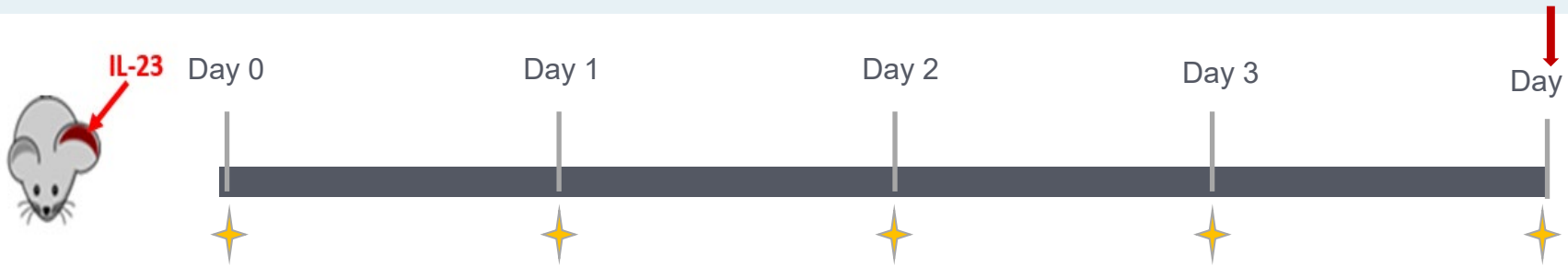
- Human IL-17 s.c. challenge induced systemic and skin production of CXCL1
- Oral administration of **PN-881** significantly reduced CXCL1 responses in serum and skin

Protagonist Therapeutics

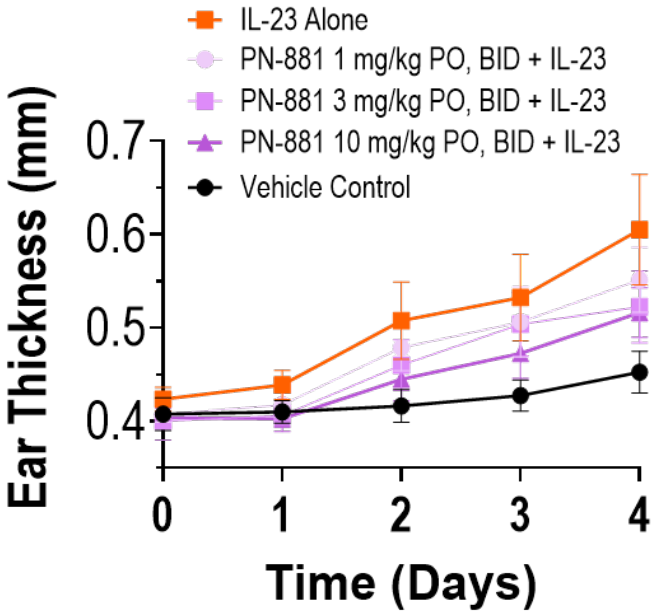
1. Manrique M, et al. Presented at the European Academy for Dermatology and Venereology (EADV) Congress. September 17-20, 2025, Paris, France.

Oral PN-881 in the Rat IL-23-induced Skin Inflammation Efficacy Model[1]

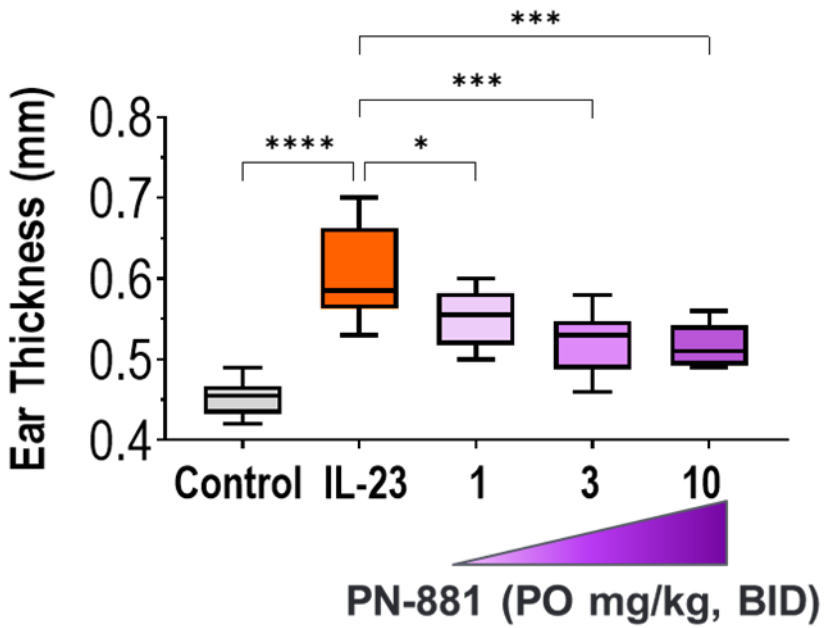
PN-881 Significantly Reduces IL-23-induced Ear Thickness After Oral Administration



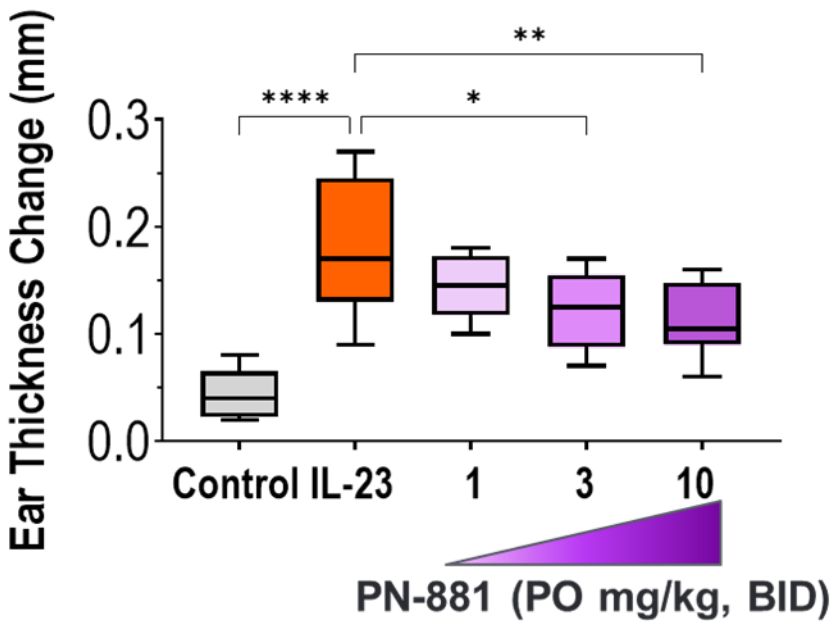
Ear Thickness Over Time



Ear Thickness (Day 4)



Ear Thickness Change



*p<0.05, **p<0.001, ****p<0.0001. Data points depict mean ± standard deviation. Boxes depict median and interquartile ranges; bars depict min. and max.

1. 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 (NCT07153146): Five-Part Phase 1 Study in Healthy Human Volunteers

Healthy Human Volunteers
N = 142 (estimated)

Eligibility:
- 18-65 years old
- Healthy male and female participants of non-childbearing potential
- Body mass index (BMI): 18-32 kg/m² (inclusive) at screening
- Male participants with female partners of childbearing potential must agree to use highly effective contraception during the study and for 90 days after the last dose

Primary endpoint:
- Incidence and severity of treatment-emergent adverse events (predose to 7 days after last dose)

Secondary endpoints:
- Pharmacokinetic and pharmacodynamic measurements

Part 1: Single Ascending Dose (SAD)
(Randomized to PN-881 or Placebo)

Study Start Date: Oct ’25

Additional Dosing Levels

Dose Level S1

Part 2: Multiple Ascending Dose (MAD)
(Randomized to PN-881 or Placebo)

Additional Dosing Levels

Dose Level M1

Part 3: Assessment of Solid Dose Formulation

Part 4: Effect of Food on Solid Dose Formulation

Part 5: Multiple Dose Pharmacokinetics of Solid Dose Formulation

Primary Completion Date: Jun ’26

Protagonist Therapeutics

What We Hope to Learn from the PN-881 Phase 1 Study

- Safety and tolerability profile of PN-881 following single and multiple dosing
- Assess PN-881 pharmacokinetics to support once-daily dosing
- Selection of tablet formulation to progress into phase 2 studies
- PN-881 exposures will guide doses for phase 2 and design of the phase 2 study

PN-881: Near-Term Clinical Development Plan

Oral IL-17 Antagonist

2H 2025	1H 2026	2H 2026	1H 2027	2H 2027
❖ **EADV'25 Meeting Oral Presentation** ❖ Phase 1 Initiation	❖ **Phase 1 Topline Results**	❖ **Phase 2 PsO Initiation**	❖ **Phase 2 PsO Interim Analysis**	❖ **Phase 2 HS Initiation**

EADV, European Academy of Dermatology and Venereology; HS, hidradenitis suppurativa; PsO, plaque psoriasis

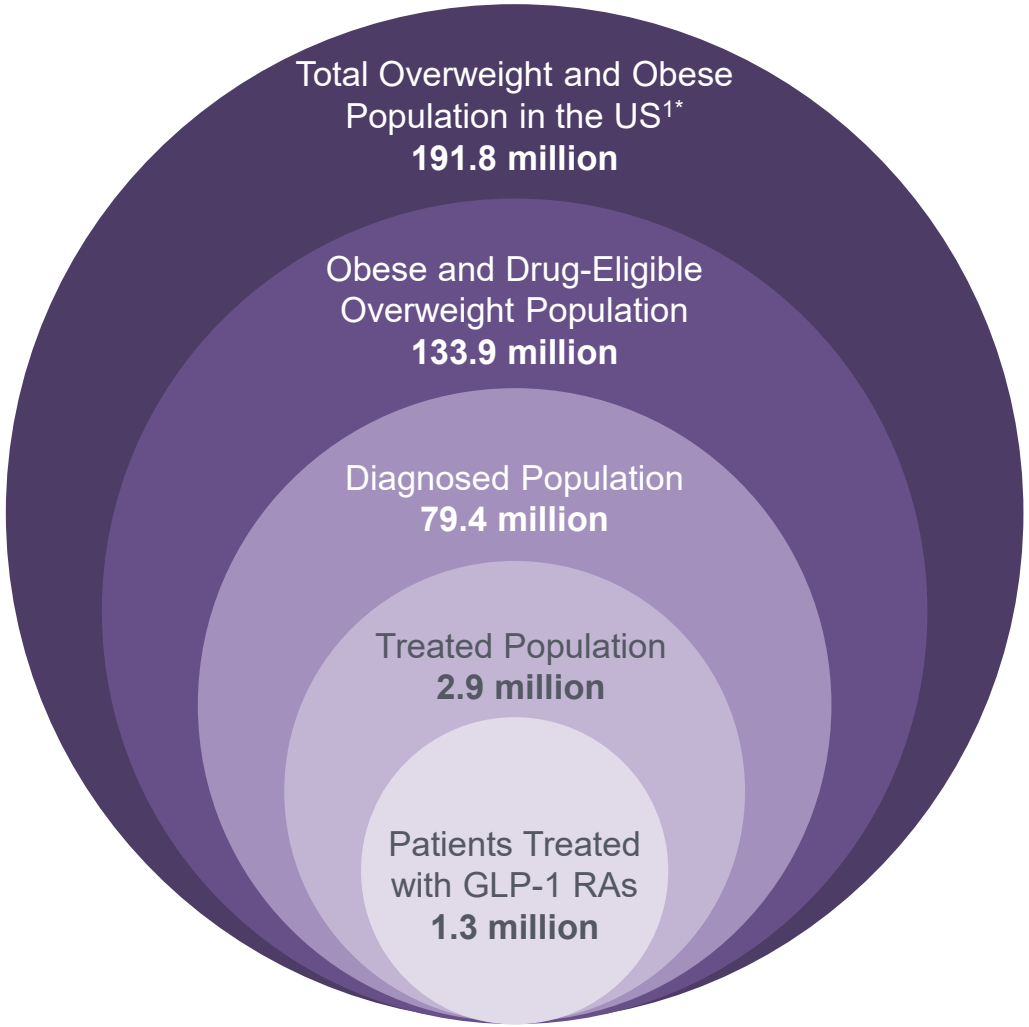
Protagonist Therapeutics

PN-477: A Novel GLP-1R/GIPR/GCGR Triple Agonist Peptide Development Candidate

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

Obesity: Unprecedented Pharmaceutical Opportunity in the US and Worldwide

Only ~2% of Eligible Patients Receive Drug Treatment



- Obesity is a global epidemic
  - In 2024, nearly **40% of Americans were obese or considered drug-eligible overweight**[1]
- Approved drugs: Injectable peptides
- Current challenges with anti-obesity drugs[1]
  - Early days & limited options
  - Adverse effects
  - Convenience; needle avoidance
- **'Oral' and 'more effective' agent an attractive option for a chronic condition**

Protagonist Therapeutics

***Total Population:** overweight (25≤BMI<30) and obese (BMI≥30) **Drug-eligible Population:** obese (BMI≥30) and drug-eligible overweight (27≤BMI<30 with at least one weight-related comorbidity) **Treated Population:** receiving noradrenergic anoretics (54%), GLP-1 RAs (43%), noradrenergic FDCs (3%), lipase inhibitors (<1%).

[1] Clarivate Disease Landscape & Forecast – Obesity/Overweight (Nov 2024).

Desirable Features for Next Generation Anti-Obesity Candidate

- Currently approved therapies are injectables
  - Semaglutide (Wegovy®): Mono GLP-1R agonist – 13.7% body weight loss[1]
  - Tirzepatide (Zepbound®): Dual GLP-1R and GIPR agonist – 20.2% body weight loss[1]
- Retatrutide: An injectable triple agonist in Ph 3 development

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, Horn DB, le Roux CW, Ho W, Falcon BL, Gomez Valderas E, Das S, Lee CJ, Glass LC, Senyucel C, Dunn JP; SURMOUNT-5 Trial Investigators. *N Engl J Med*. 2025;393(1):26-36.

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

Optionality for Oral or Subcutaneous Dosing

PN-477o

ORAL Triple-Agonist
Once-daily Dosing

PN-477sc

Injectable Triple-Agonist
Once-weekly Dosing

Protagonist Therapeutics

PN-477 Triple Agonist (GLP-1R, GIPR, GCGR) Peptide as Development Candidate

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 supports once-a-day oral dosing** ✓ • **Plasma PK profile supports once-a-week subcutaneous dosing** ✓

Protagonist Therapeutics

GI: Gastrointestinal; PK: Pharmacokinetic

PN-477: A Highly Potent Triple GLP-1/GIP/GCG Receptor Agonist Designed to Provide Weight Loss Profile of Retatrutide and GI Tolerability of Tirzepatide

	Human EC_{90} (nM)			Mouse EC_{90} (nM)		
	GLP-1R	GIPR	GCGR	GLP-1R	GIPR	GCGR
Semaglutide[1,‡] (Novo **Mono** GLP-1R)	74	NA†	NA†	6.1	NA†	NA†
Tirzepatide[2,‡] (Eli Lilly **Dual** GLP-1R/GIPR)	269	17x → 16	NA†	21	867	NA†
Retatrutide[3,‡] (Eli Lilly **Triple** GLP-1R/GIPR/GCGR)	103	6x → 17	83	8.3	493	102
PN-477	**49**	**17x → 2.7**	**56**	**17**	**133**	**1092**

‡Sourced from *MCE Cat. HY-114118 (Semaglutide); 1PlusChem Cat. 1P01MVTY (Tirzepatide); MCE Cat. HY-P3506 (Retatrutide)*

† ***NA: Not Active***

- Human EC_{50} potencies:

Human EC_{50} (nM)	GLP-1R	GIPR	GCGR
PN-477	4.6	0.39	15
Retatrutide	12.2	1.5	21

- Higher GIPR potency may be favorable for better GI tolerability[4,5]

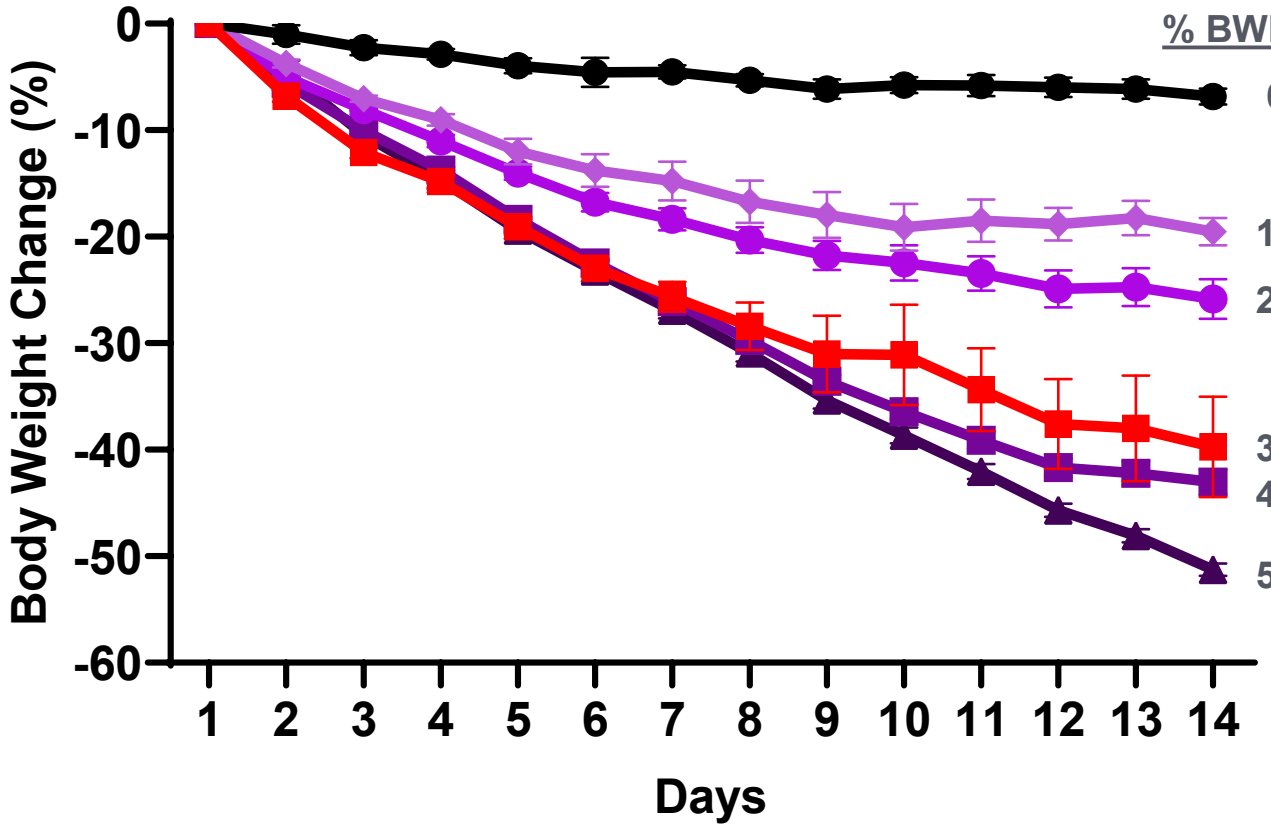
Protagonist Therapeutics

[1] Lau J, J Med Chem 2015; [2] Coskun T, Mol Metab 2018; [3] Coskun T, Cell Metab 2022; [4] Campbell JE, Cell Metabolism 2023; [5] El K, Sci Adv 2021

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

DIO Mice Study #1

% Body Weight Change, PO: Days 1-14



% BWL by D14	
6.8	Vehicle Control (PO, QD)
19.5	PN-477o (PO 3 mg/kg, QD)
25.9	PN-477o (PO 10 mg/kg, QD)
39.7	Retatrutide (**SC** 30 nmol/kg, Q3D)*
43.1	PN-477o (PO 30 mg/kg, QD)
51.3	PN-477o (PO 90 mg/kg, QD)

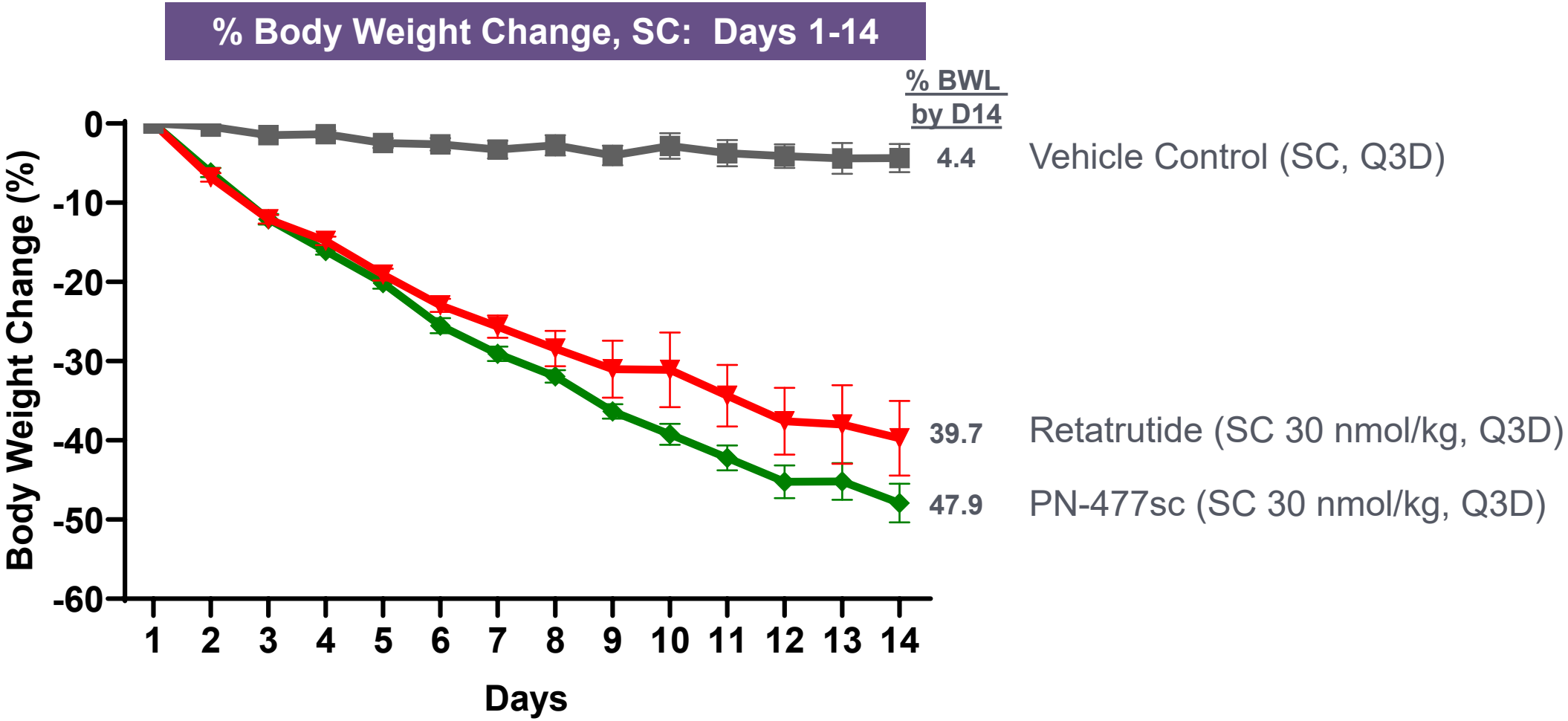
* Retatrutide SC 30 nmol/kg dose is the highest dose reported for DIO mouse efficacy study
(Cell Metabolism 34, 1234–1247, September 6, 2022)

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

Protagonist Therapeutics

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

DIO Mice Study #1



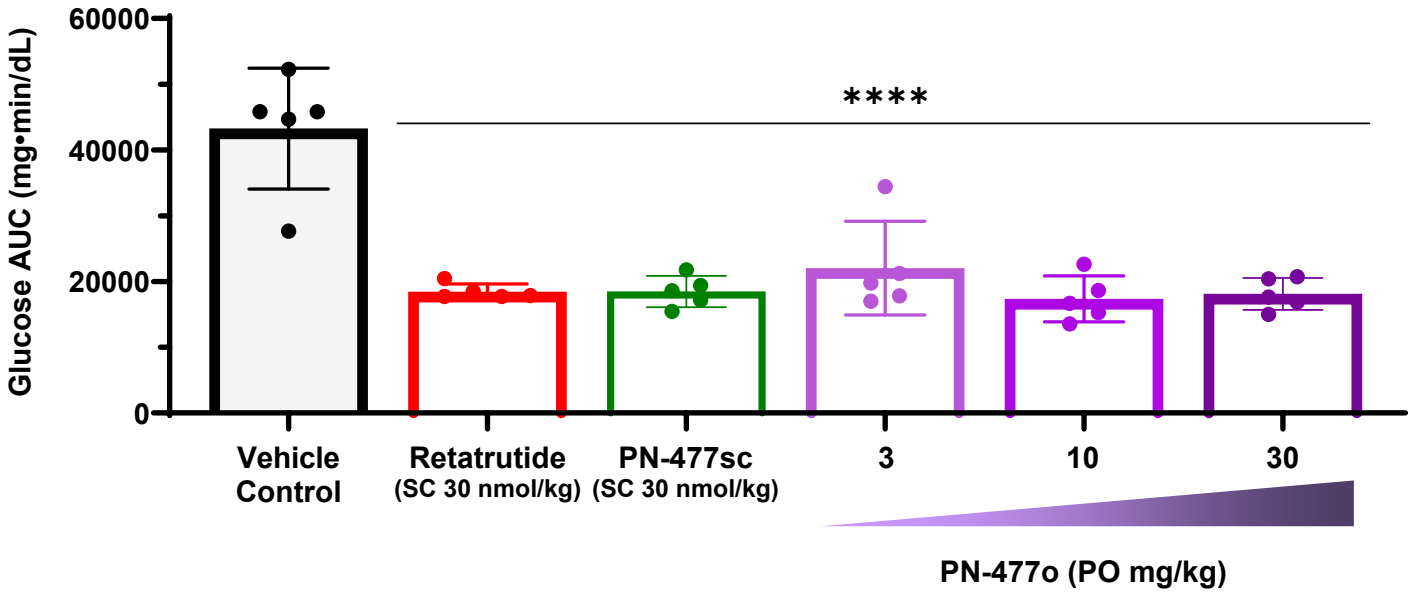
Protagonist Therapeutics

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

PN-477 (Oral and SC) Improves Glycemic Control after Glucose Challenge

DIO Mice Study #3

OGTT in DIO Mice
Single Dose, PO and SC, 2-hr PD



- Glycemic control is significantly improved in DIO mice after PN-477 PO or SC when compared to the vehicle control
- Profiles consistent with retatrutide

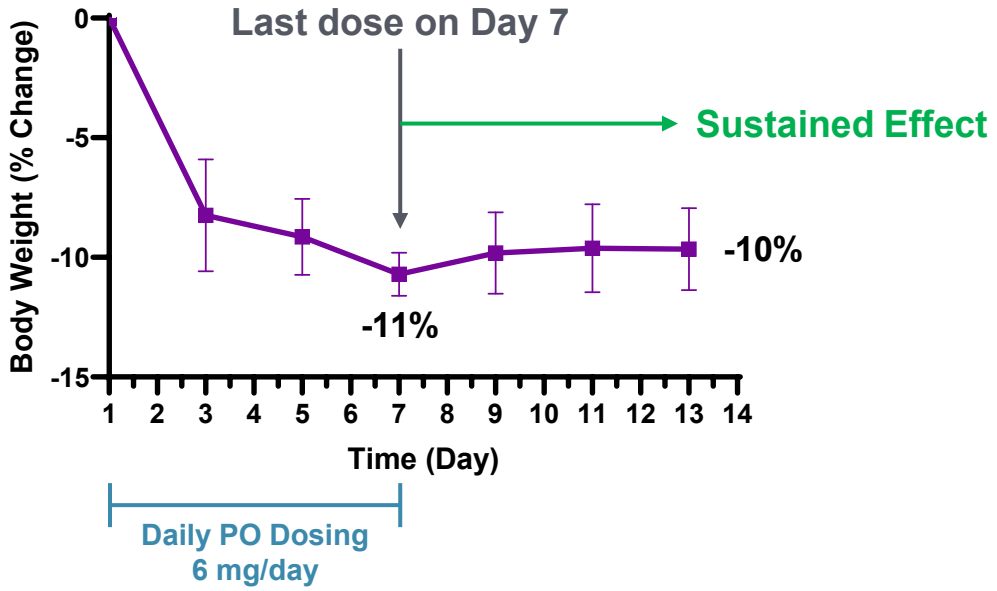
Protagonist Therapeutics

****p<0.0001; One way ANOVA; n=7. Bars depict mean ± SEM. Retatrutide was synthesized by Protagonist.
OGTT: oral glucose tolerance test; DIO: diet induced obese; PO: Per Os (oral); SC: subcutaneous; PD: Pharmacodynamics; AUC: area under curve

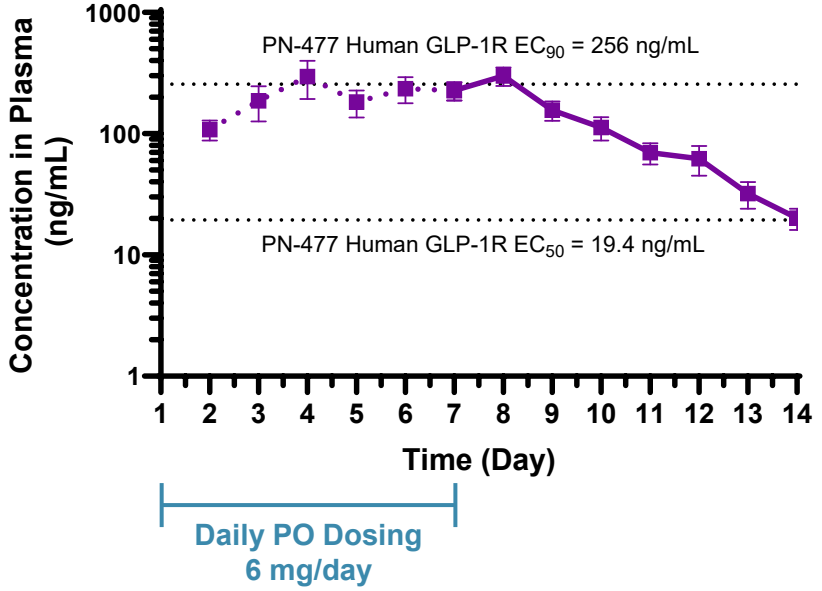
11% BW Loss by Day 7 in Cynomolgus Monkeys after 7-Day Oral Dosing of PN-477o

Weight Loss Sustained for 6 Days After Last Dose

Cyno % BW Change, PO



Cyno PK C_{trough} Day 1-7, PO



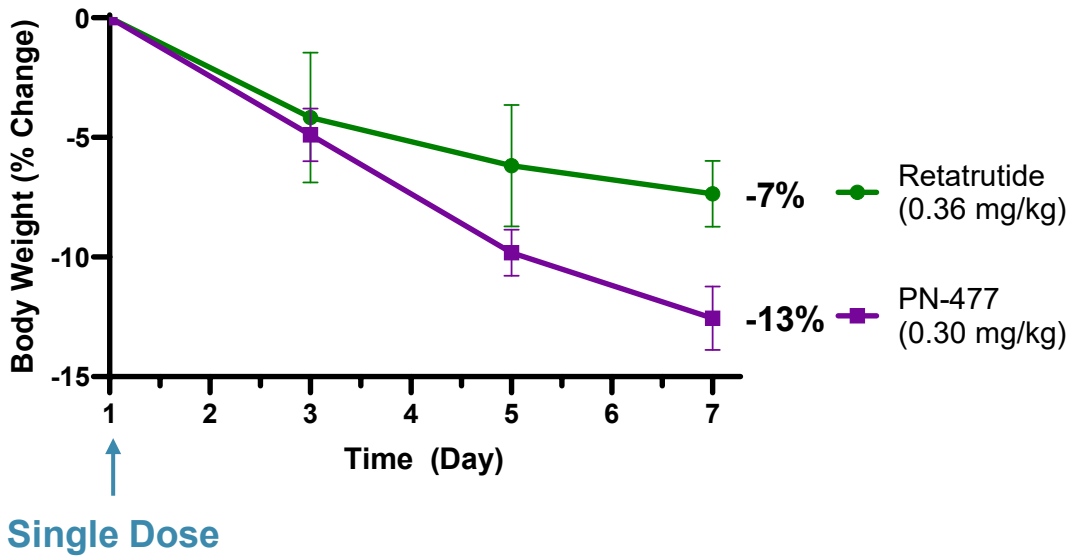
- PN-477o PK profile suggests once daily human dosing
- Body weight loss was sustained for 6 days post-last dose

BW: Body Weight; PO: Per Os (oral); PK: Pharmacokinetics

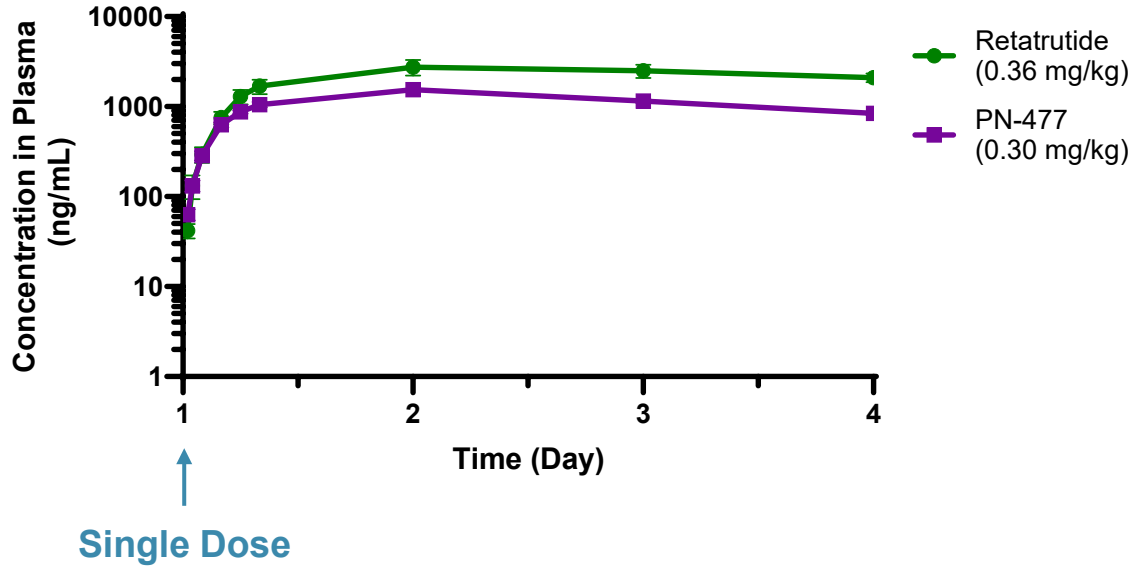
13% BW Loss by Day 7 in Normal Monkeys after Single SC Dose of PN-477

PN-477 Vs. Retatrutide

Cyno % BW Change, SC



Cyno PK, SC



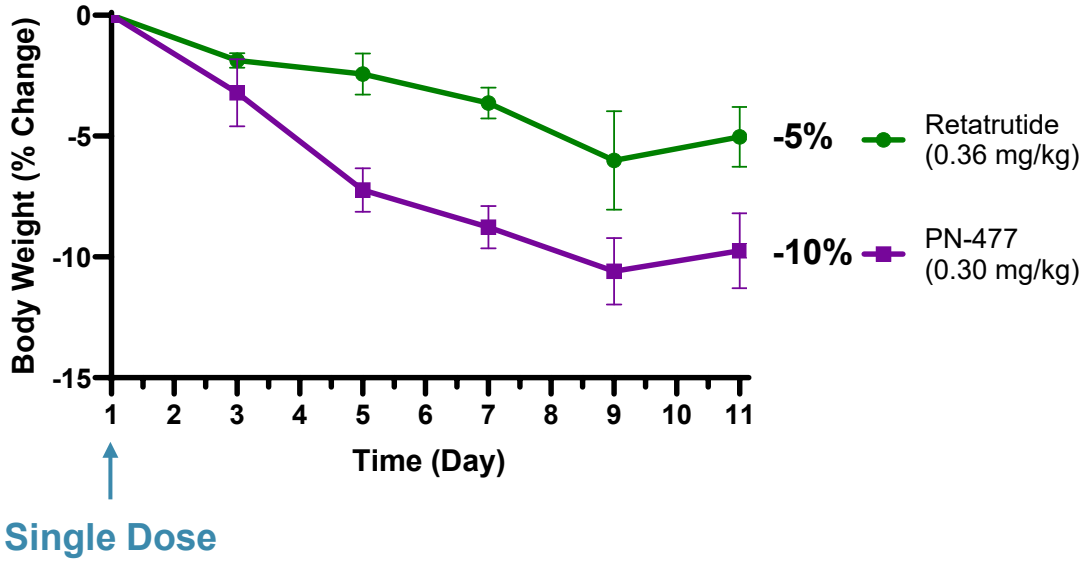
PN-477sc PK profile suggests once weekly human dosing

BW: Body Weight; PK: Pharmacokinetics; SC: subcutaneous

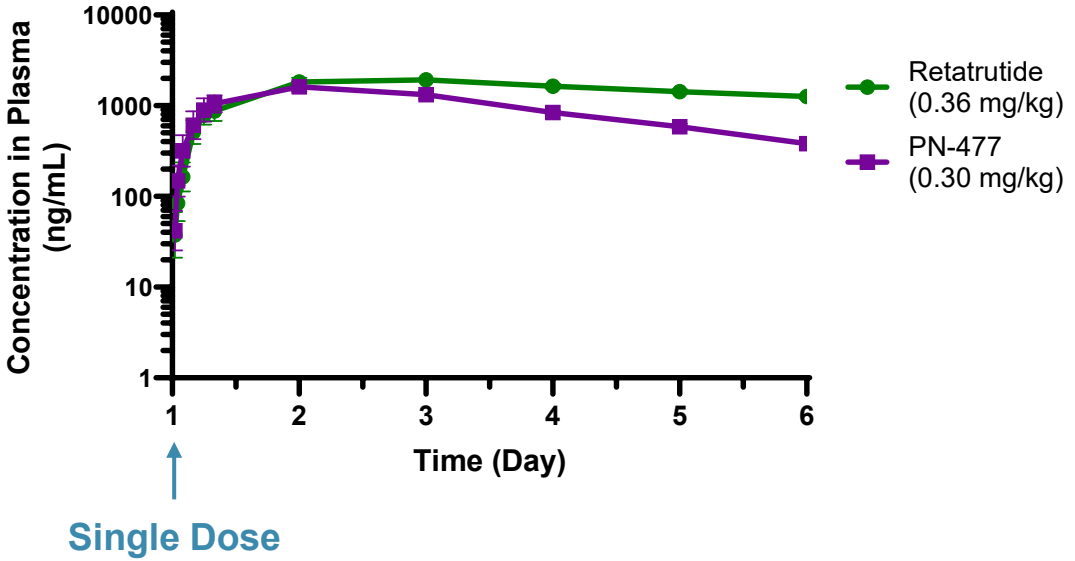
10% BW Loss by Day 11 in Normal Beagle Dogs after Single SC Dose of PN-477

PN-477 Vs. Retatrutide

Dog % BW Change, SC



Dog PK, SC



PN-477sc PK profile suggests once weekly human dosing

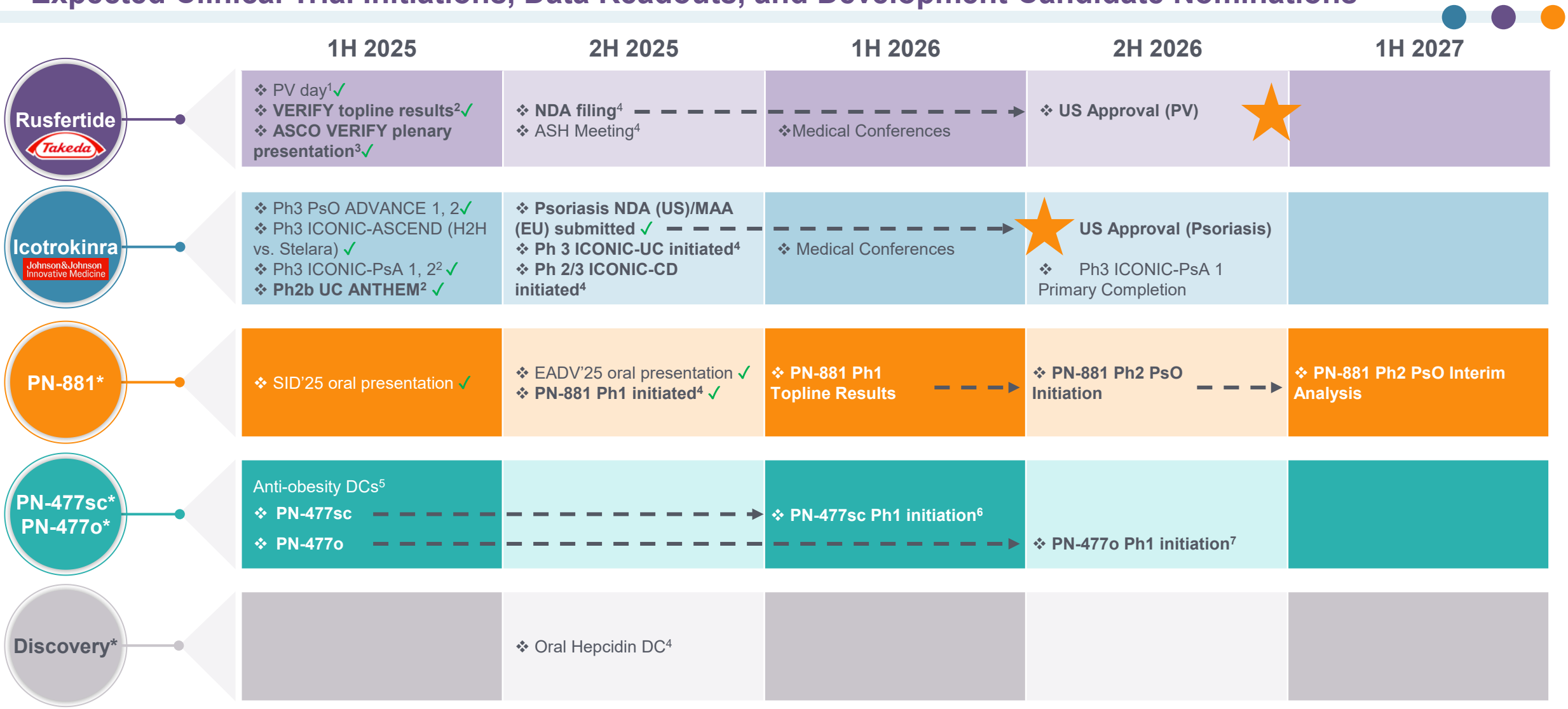
BW: Body Weight; PK: Pharmacokinetics; SC: subcutaneous

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, 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

Major Upcoming Catalysts in 2H 2025 Through 1H 2027

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



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*Fully owned by Protagonist Therapeutics, Inc.

1. February 6, 2025 2. March 2025 3. June 1, 2025 4. Q4 2025 5. June 30, 2025 6. Q2 2026 7. Q3 2026

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Thank you