Protagonist Therapeutics

COMPANY OVERVIEW

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

October 9, 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.

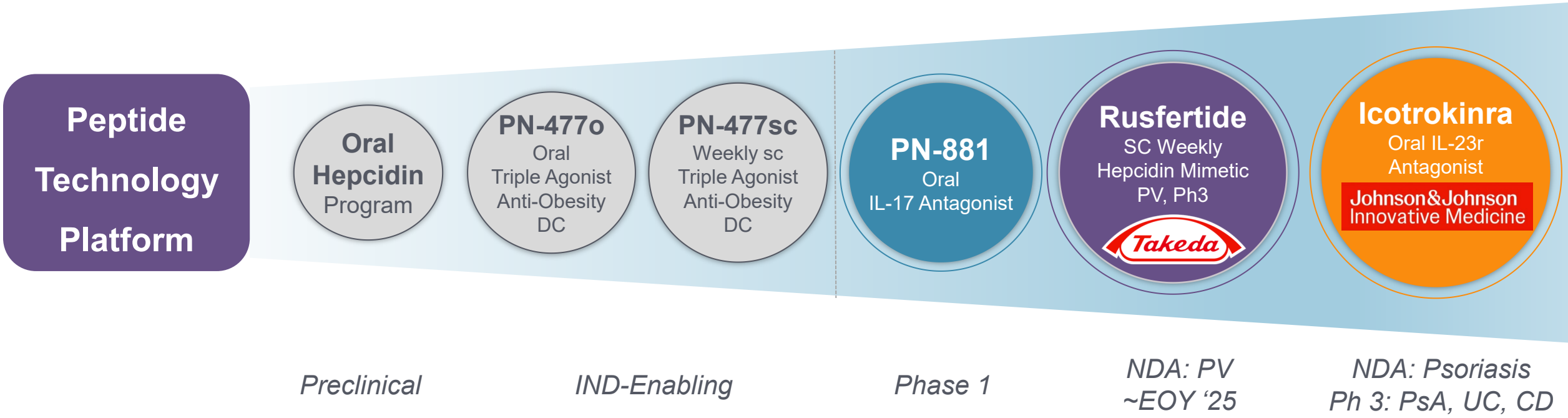
The forward-looking statements made in this presentation involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the 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.

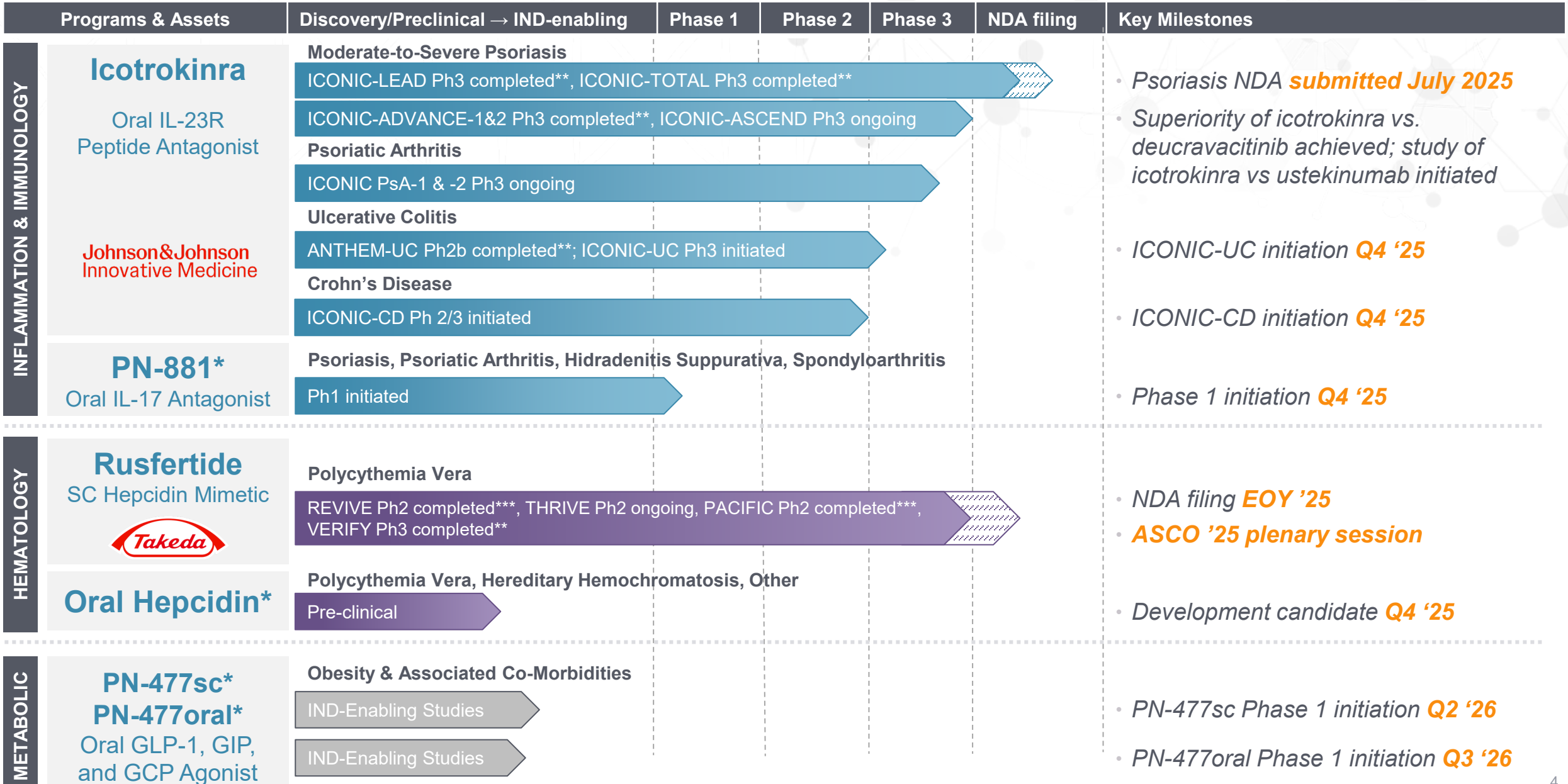
A Peptide Therapeutics Company

Protagonist Therapeutics

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



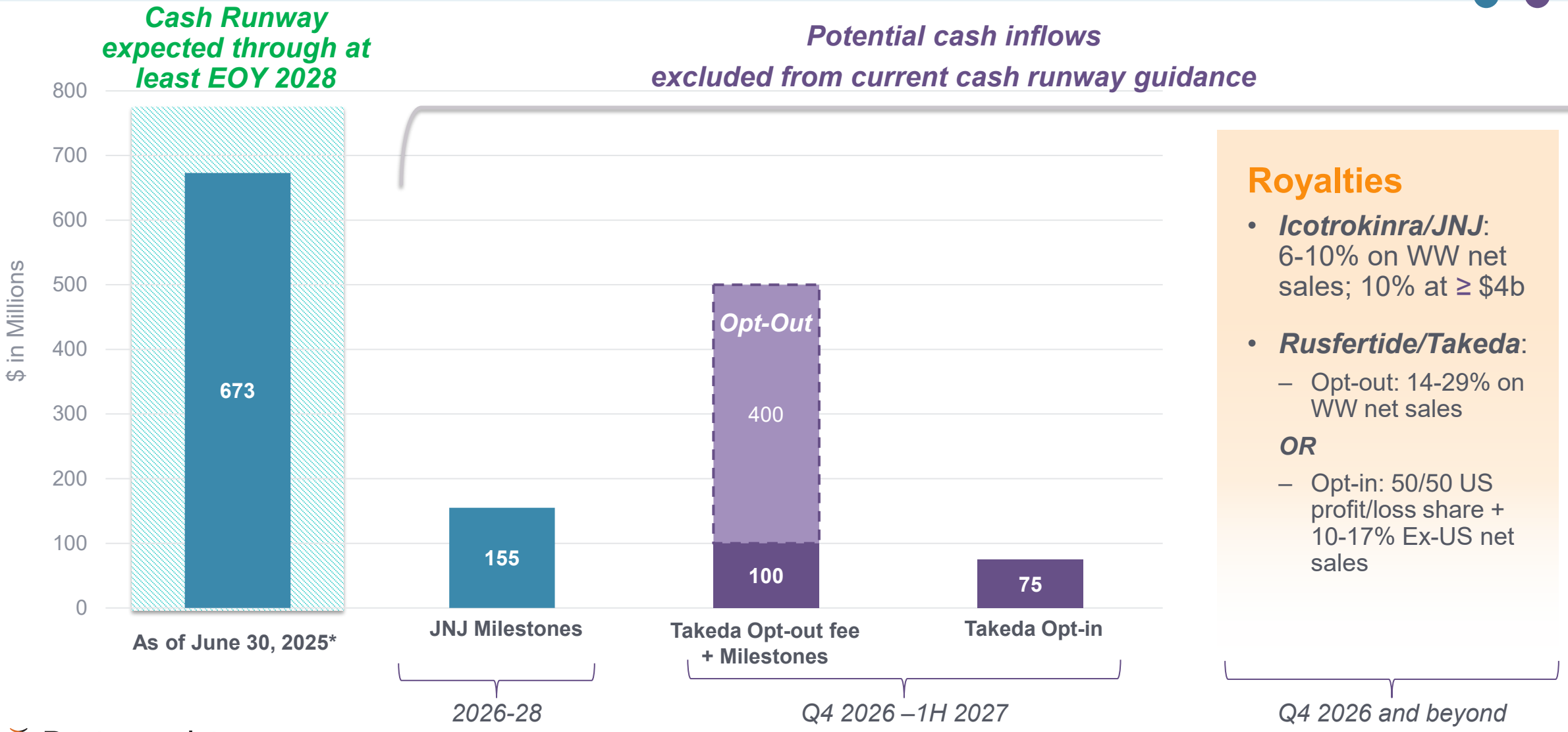
Pipeline of Proprietary and Partnered Programs



*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

Protagonist Therapeutics

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

Capital Allocation Considerations

- **Internal 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***	

Protagonist Therapeutics

* $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

Protagonist Therapeutics

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

Protagonist Therapeutics

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.

Protagonist Therapeutics

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 ✓
- **ICONIC-LEAD** Ph3, n = 684, in moderate-to-severe psoriasis ✓
- **ICONIC-TOTAL** Ph3, n = 311, psoriasis in special areas of body ✓
- **ICONIC-ADVANCE 1** Ph3, n = 774, Icotrokinra vs. Deucravacitinib ✓
- **ICONIC-ADVANCE 2** Ph3, n = 731, Icotrokinra vs. Deucravacitinib ✓
- **Pustular/Erythrodermic Psoriasis** Ph3, n = 19 · Ongoing
- **ICONIC-ASCEND** Ph3, n = 675, Icotrokinra vs. Ustekinumab · Ongoing

Bissonnette R. et al. ***New Engl Med***; 2024;390:510-521

Psoriasis
NDA submitted July 2025

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

Protagonist Therapeutics

Protagonist Therapeutics

2025 EADV Meeting (17-20 September; Paris, France)

Icotrokinra Updates:

- ICONIC-ADVANCE 1 & 2
- ICONIC-LEAD

Icotrokinra Psoriasis Clinical Studies Update: EADV'25 Meeting

- **Phase 3 ICONIC-ADVANCE 1 & 2 studies[1]** (Link to presentation here)
  - **Icotrokinra met both co-primary endpoints compared to placebo at Week 16 with similar adverse event rates and showed superiority to deucravacitinib at multiple timepoints in adult patients**
    - Icotrokinra showed superior skin clearance vs placebo (Week 16) and deucravacitinib (Weeks 16 and 24)
    - Icotrokinra demonstrated similar adverse event rates (AEs) to placebo, with no new safety signals identified
    - Icotrokinra AE rates were numerically lower vs deucravacitinib through Week 24
- **Phase 3 ICONIC-LEAD study[2] (**Link to presentation here)
  - **Icotrokinra demonstrated sustained skin clearance and a favorable safety profile through Week 52 with no new safety signals identified in the ICONIC-LEAD drug withdrawal/re-retreatment study**
    - At Week 52, adult icotrokinra PASI 90 responders re-randomized to icotrokinra at Week 24 had superior maintenance of PASI 90 response versus those re-randomized to placebo (84% vs 21%; $p<0.001$)
    - At Week 52, 86% of adolescents who received icotrokinra for the full 52 weeks and 77% of those who switched from placebo to icotrokinra at Week 16 achieved PASI 90 response
    - ICONIC-LEAD Week 16 primary endpoint data previously presented at the American Academy of Dermatology 2025 Congress[3]

1. Stein Gold, L et al. Icotrokinra Demonstrated Superior Responses Compared with Placebo and Deucravacitinib in the Treatment of Moderate-to-Severe Plaque Psoriasis : Results Through Week 24 of the Phase 3 ICONIC-ADVANCE 1 & 2 Studies. Oral presentation (Presentation FC01.1G) at the European Academy of Dermatology and Venereology Congress (EADV). September 2025.

2. Soung, J et al. Maintenance of Response with Icotrokinra, a Targeted Oral Peptide, for the Treatment of Moderate-to-Severe Psoriasis : Randomized Treatment Withdrawal in Adults (weeks 24-52) and Continuous Treatment in Adolescents (Through Week 52) From the Phase 3, ICONIC-LEAD Trial. Late-breaking research oral presentation (Presentation #D1T01.2B) at the European Academy of Dermatology and Venereology Congress (EADV). September 2025.

3. Bissonnette, R et al. Icotrokinra, a Targeted Oral Peptide That Selectively Blocks the Interleukin-23–Receptor, for the Treatment of Moderate-to-Severe Plaque Psoriasis: Results Through Week 24 of the Phase 3, Randomized, Double-blind, Placebo-Controlled ICONIC-LEAD Trial. Late-breaking research presentation (Abstract #66708) at the American Academy of Dermatology (AAD) 2024 Annual Meeting. March 2025.

Protagonist Therapeutics

ICONIC-ADVANCE 1 & 2: Key Takeaways

2025 EADV Meeting (17-20 September; Paris, France)

- In both of the pivotal Phase 3 ICONIC-ADVANCE 1 & 2 studies, adults with moderate-to-severe plaque PsO receiving icotrokinra (ICO) consistently demonstrated superior skin clearance and symptom relief vs PBO and Deucra:

- **ICO demonstrated significantly higher rates vs Deucra:**
  - Clear/almost clear skin
  - Completely clear skin *(~2-fold or greater)*
  - Symptom resolution

- **Favorable ICO safety:**
  - AE profile similar to PBO
  - Overall AE & infection rates lower than Deucra
  - No safety signal

ICO, a targeted oral peptide that binds and inhibits the IL-23R, has the potential to provide high rates of skin clearance and PsO symptom relief with a favorable safety profile in a once-daily pill

Protagonist Therapeutics

AE=adverse event, Deucra=deucravacitinib, IL-23R=interleukin-23 receptor, PBO=placebo, PsO=psoriasis.

ICONIC-LEAD: Key Takeaways

2025 EADV Meeting (17-20 September; Paris, France)

- In the pivotal phase 3 ICONIC-LEAD study evaluating the targeted oral peptide icotrokinra (ICO) through 1 year in adults & adolescents with moderate-to-severe plaque PsO:

Continuous ICO demonstrated superior maintenance of skin response among adult W24 ICO responders:

- *89% and 84% maintained PASI 75 and PASI 90, respectively, at W52*
- *LOR vs ICO withdrawal: Not reached vs 17 weeks (PASI 75) or 10 weeks (PASI 90)*

Continuous ICO demonstrated robust and durable skin clearance rates in *adolescents* through W52:

- *PASI 90: 86%*
- *PASI 75: 95%*
- *IGA 0/1: 82%*

- **ICO AE profile through W52 was consistent with that observed through W16**

- No ICO safety signal was identified through W52

Protagonist Therapeutics

AE, adverse event; **IGA,** Investigator's Global Assessment; **LOR,** loss of response; **PASI,** Psoriasis Area and Severity Index; **PsO,** psoriasis; **W,** week.

Protagonist Therapeutics

Icotrokinra, a Targeted Oral Peptide that Selectively Blocks IL-23 Receptor Activation, in Moderately to Severely Active Ulcerative Colitis: Week 12 Results from the Phase 2b, Randomized, Double-blind, Placebo-controlled, Treat-through, Dose-ranging ANTHEM-UC Trial

UEGW 2025, Berlin, Germany & Online, October 4-7, 2025

Background and Objective

- Despite the availability of monoclonal antibodies and other agents targeting key inflammatory mediators, many patients with ulcerative colitis have inadequately controlled disease or do not tolerate available treatments

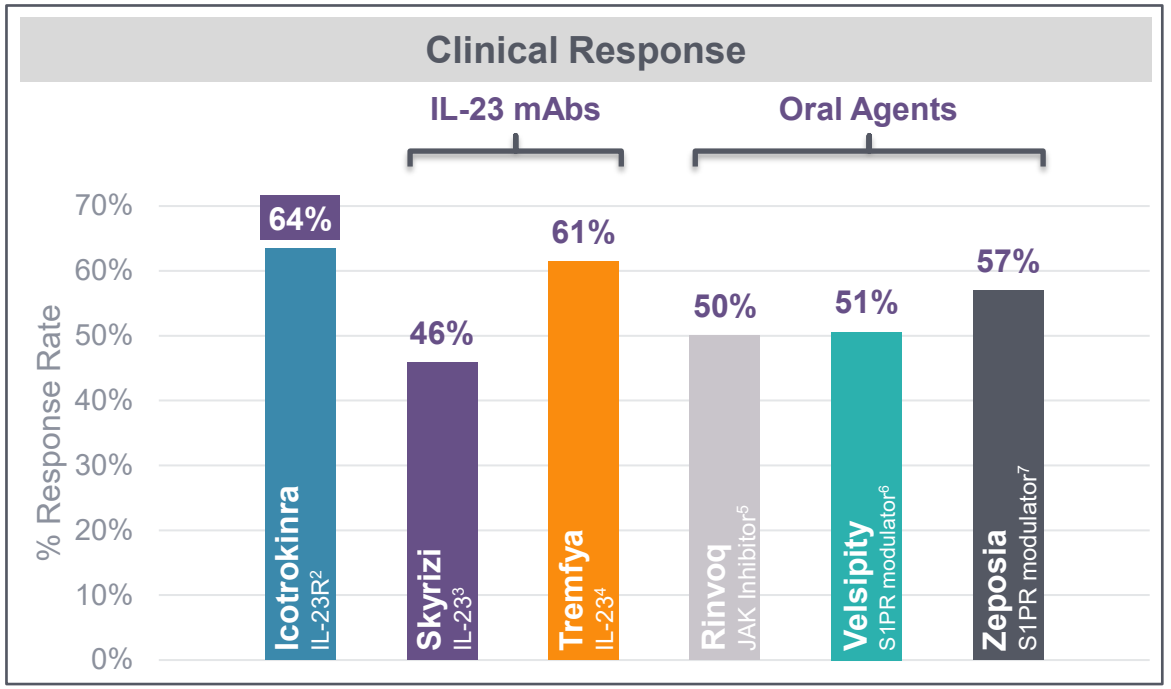
- Icotrokinra has the potential to offer patients with moderately to severely active ulcerative colitis the standout combination of high efficacy and favorable safety profile with the simplicity of a once-daily oral pill

- Icotrokinra (formerly JNJ-2113) is a first-in-class investigational targeted oral peptide that potently and selectively blocks the IL-23 receptor at the site of inflammation

- ANTHEM-UC (NCT06049017) evaluated the efficacy and safety of three doses of once-daily oral icotrokinra in adult participants with moderately to severely active ulcerative colitis

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

Clinical Response



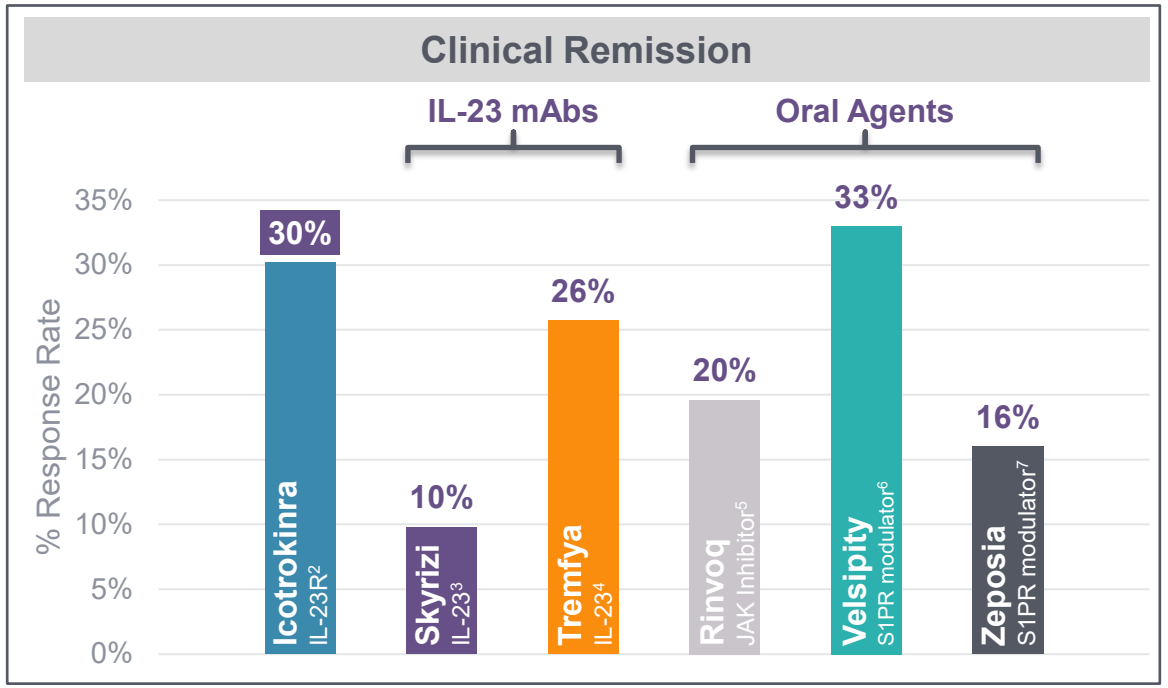
Agent	Endpoint Timeframe	Placebo Response (%)
Icotrokinra	Wk 12	27.0
Skyrizi	Wk 12	20.0
Tremfya	Wk 12	27.6
Rinvoq	Wk 8	13
Velsipity	Wk 12	32.5
Zeposia	Wk 8	37

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

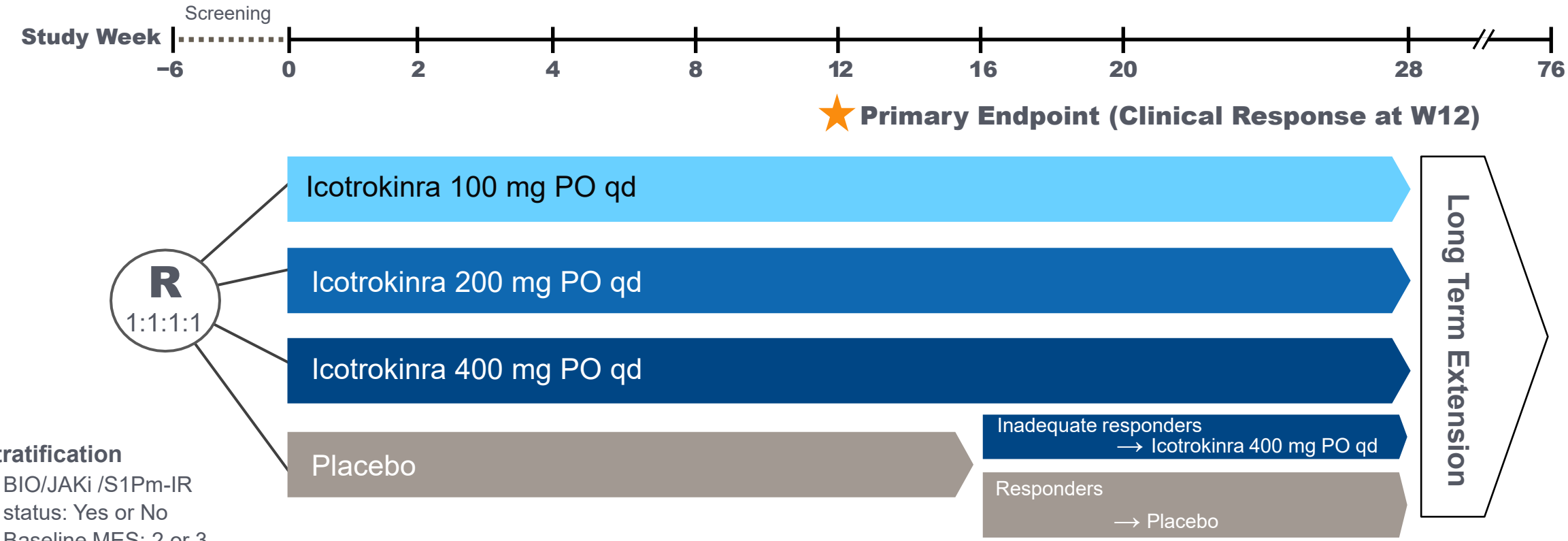
1. Cross trial (not head-to-head) comparisons of unadjusted (ie, non-placebo adjusted) remission data from phase 2 studies.
2. Icotrokinra (JNJ-2113) highest dose (in mg; PO qd) with clinical remission at Wk 12 (ie, Mayo stool frequency subscore of 0 or 1 and not increased from induction baseline, a 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 Study Design

Key Eligibility Criteria

- Diagnosed UC of ≥12 weeks duration and a Modified Mayo score (mMS) of 5–9, inclusive
- Mayo endoscopy 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

Testing Procedure and Statistical Considerations

- **Primary Endpoint**
  - Clinical response vs placebo at Week 12

- **Secondary Endpoints (all vs placebo at Week 12)**
  - Clinical remission
  - Symptomatic remission
  - Endoscopic improvement
  - Histologic-endoscopic mucosal improvement (HEMI)

☑ Study powered to detect a treatment difference between icotrokinra 400 mg and placebo for the primary endpoint; it was not powered for the secondary endpoints

☑ Statistical testing was conducted sequentially: if a comparison was p≥0.05, all subsequent comparisons were not significant and nominal p-values are presented

Demographics and Baseline Disease Characteristics

	Placebo	Icotrokinra 100 mg QD	Icotrokinra 200 mg QD	Icotrokinra 400 mg QD	Total
Full analysis set, n	63	64	62	63	**252**
Age, years, mean (SD)	38.3 (13.8)	45.8 (14.6)	41.8 (14.6)	40.6 (14.8)	**41.6 (14.7)**
Sex, male, n (%)	35 (55.6%)	40 (62.5%)	32 (51.6%)	40 (63.5%)	**147 (58.3%)**
Race, White, n (%)	44 (69.8%)	45 (70.3%)	39 (62.9%)	42 (66.7%)	**170 (67.5%)**
UC disease duration, years, mean (SD)	8.3 (8.1)	7.4 (6.1)	7.8 (7.5)	7.6 (7.6)	**7.8 (7.3)**
Extensive disease, n (%)	27 (42.9%)	23 (35.9%)	23 (37.1%)	29 (46.0%)	**102 (40.5%)**
Modified Mayo score [max = 9], mean (SD)	6.75 (1.231)	6.55 (1.296)	6.75 (1.386)	6.49 (1.401)	**6.63 (1.327)**
Mayo endoscopic subscore of 3 (severe), n (%)	36 (57.1%)	38 (59.4%)	37 (59.7%)	37 (58.7%)	**148 (58.7%)**
Fecal calprotectin, mg/kg, median [IQR]	1467.0 [420.5; 3622.0]	1433.3 [698.0; 3121.2]	2467.0 [646.4; 4599.6]	1421.3 [584.6; 4978.6]	**1523.0 [587.0; 3816.7]**
CRP, mg/L, median [IQR]	3.0 [0.9; 7.0]	3.0 [1.1; 6.7]	5.3 [1.5; 11.3]	4.0 [1.5; 8.1]	**3.6 [1.3; 8.1]**

Protagonist Therapeutics

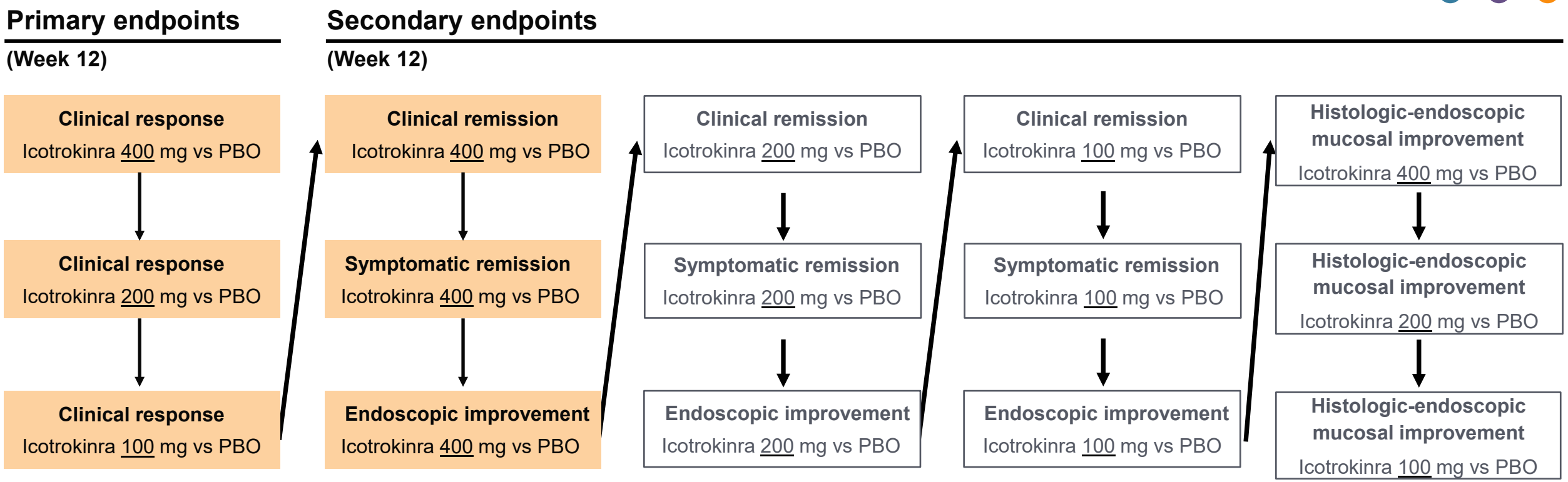
Demographics and Baseline Disease Characteristics (Continued)

	Placebo	Icotrokinra 100 mg QD	Icotrokinra 200 mg QD	Icotrokinra 400 mg QD	Total
Full analysis set, n	63	64	62	63	**252**
Baseline corticosteroid use, n (%)	21 (33.3%)	21 (32.8%)	29 (46.8%)	23 (36.5%)	**94 (37.3%)**
Baseline immunomodulator use, n (%)	16 (25.4%)	10 (15.6%)	10 (16.1%)	6 (9.5%)	**42 (16.7%)**
No history of BIO/JAKi/S1Pm-IR, n (%)	35 (55.6%)	38 (59.4%)	36 (58.1%)	34 (54.0%)	**143 (56.7%)**
History of BIO/JAKi/S1Pm-IR, n (%)	28 (44.4%)	26 (40.6%)	26 (41.9%)	29 (46.0%)	**109 (43.3%)**
IR to 1 class / mechanism[a]	22 (78.6%)	19 (73.1%)	21 (80.8%)	15 (51.7%)	**77 (70.6%)**
IR to 2 classes / mechanisms[a]	6 (21.4%)	6 (23.1%)	5 (19.2%)	14 (48.3%)	**31 (28.4%)**
IR to >2 classes / mechanisms[a]	0	1 (3.8%)	0	0	**1 (0.9%)**

Protagonist Therapeutics

a. Denominator was number of participants with a history of inadequate response or intolerance to biologics, JAK inhibitors, or S1P modulators (BIO/JAKi/S1Pm-IR)
BIO = TNFα antagonists, ustekinumab, or vedolizumab; IR = prior inadequate response or intolerance

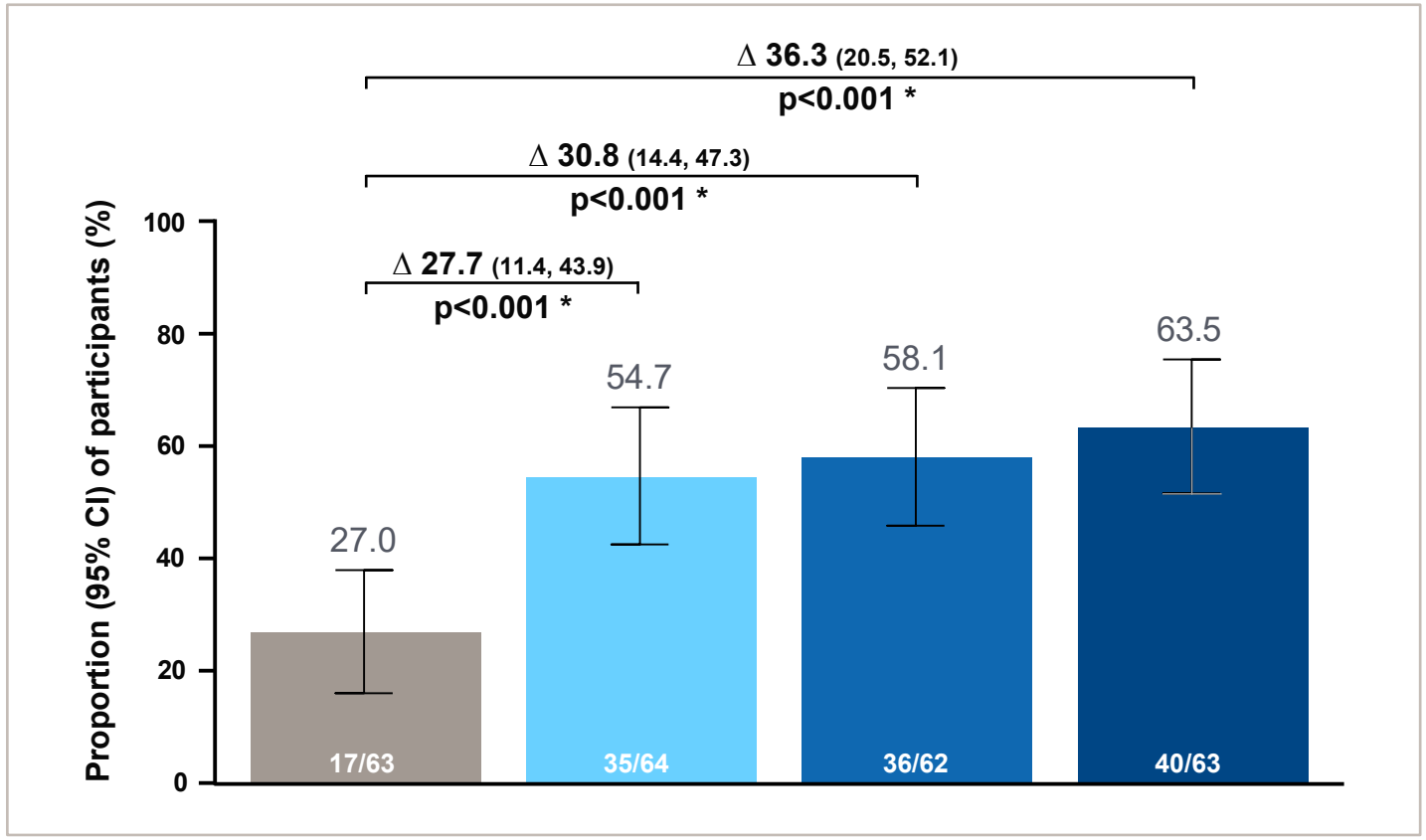
Multiple Testing Procedure and Statistical Considerations



- Statistical testing was conducted sequentially: if a comparison was $p \geq 0.05$, all subsequent comparisons were not significant, and nominal p-values are presented
- The study was powered to detect a treatment difference between icotrokinra 400 mg and placebo for the primary endpoint; it was not powered for the secondary endpoints

Protagonist Therapeutics

Primary Endpoint: Clinical Response at Week 12



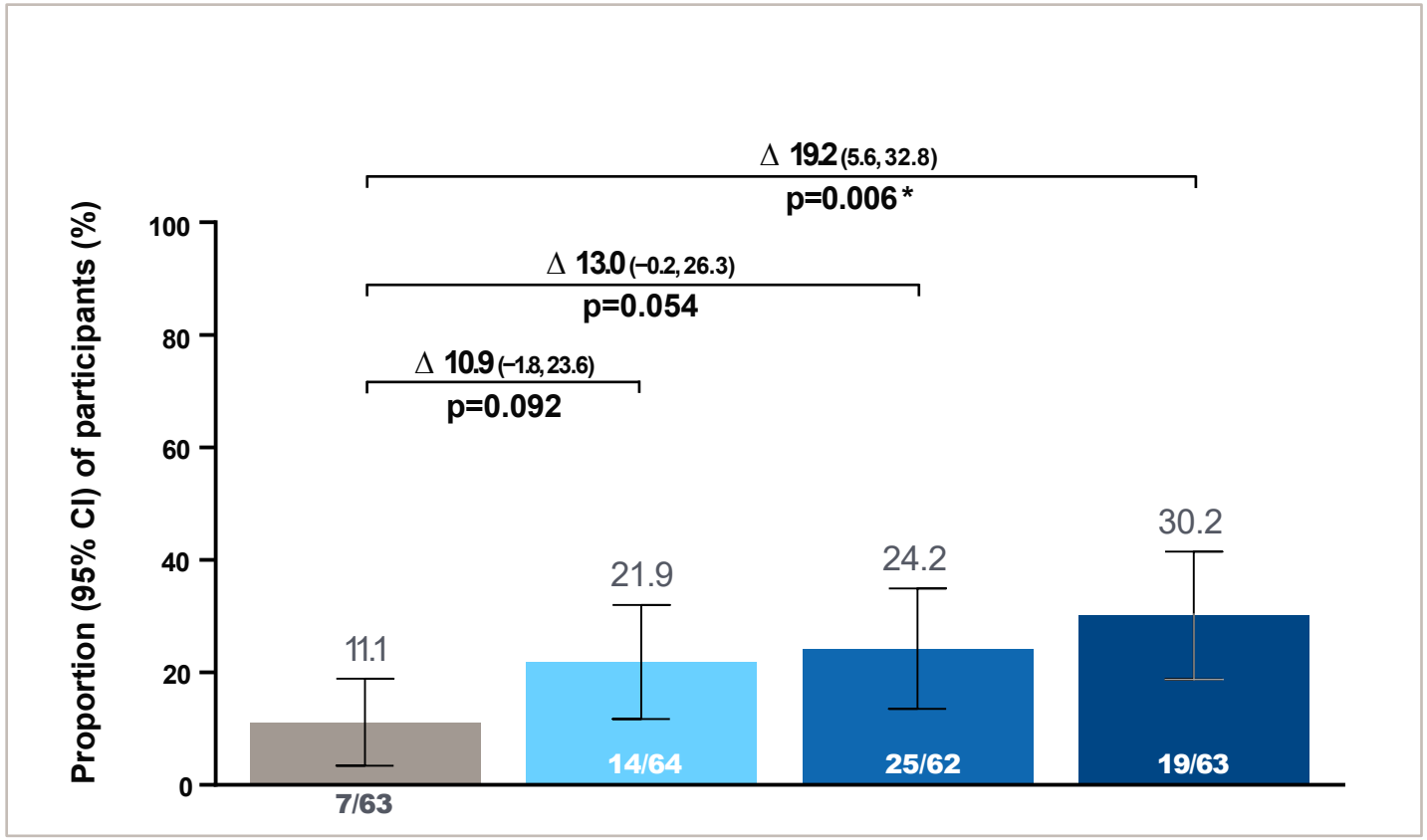
*Statistically significant based on testing procedure

Clinical response: 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 or 1

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopy subscore (moderate [2] or severe [3]).
Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders, as were participants who had missing data for the endpoint. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Protagonist Therapeutics

Clinical Remission at Week 12



Placebo

Icotrokinra 100 mg qd

Icotrokinra 200 mg qd

Icotrokinra 400 mg qd

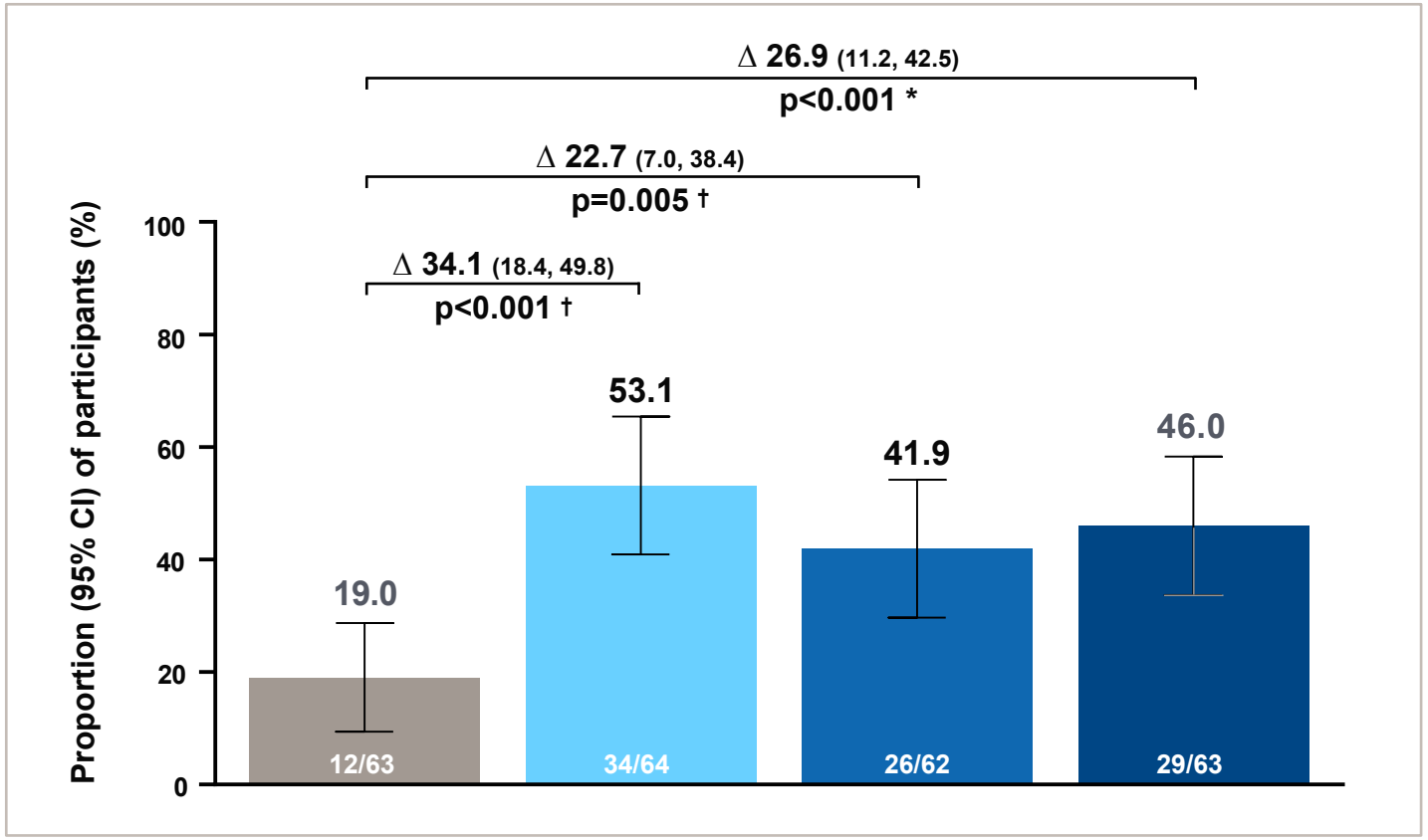
*Statistically significant based on testing procedure

Clinical remission: stool frequency subscore of 0 or 1, rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopy subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders, as were participants who had missing data for the endpoint. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Protagonist Therapeutics

Symptomatic Remission at Week 12



* Statistically significant based on testing procedure

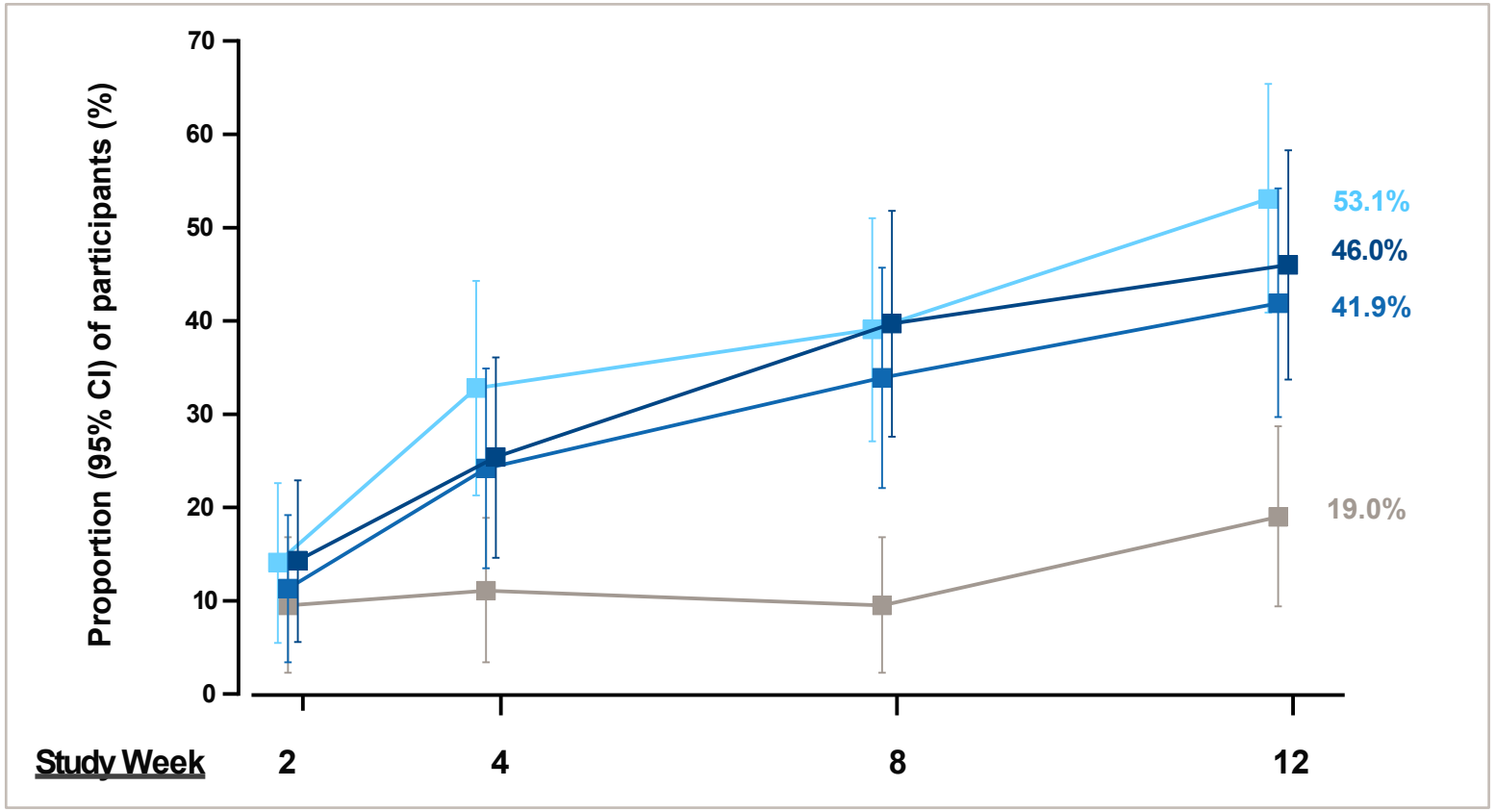
† Nominal p-value <0.05

Symptomatic remission: stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopy subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders, as were participants who had missing data for the endpoint. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Protagonist Therapeutics

Symptomatic Remission Through Week 12



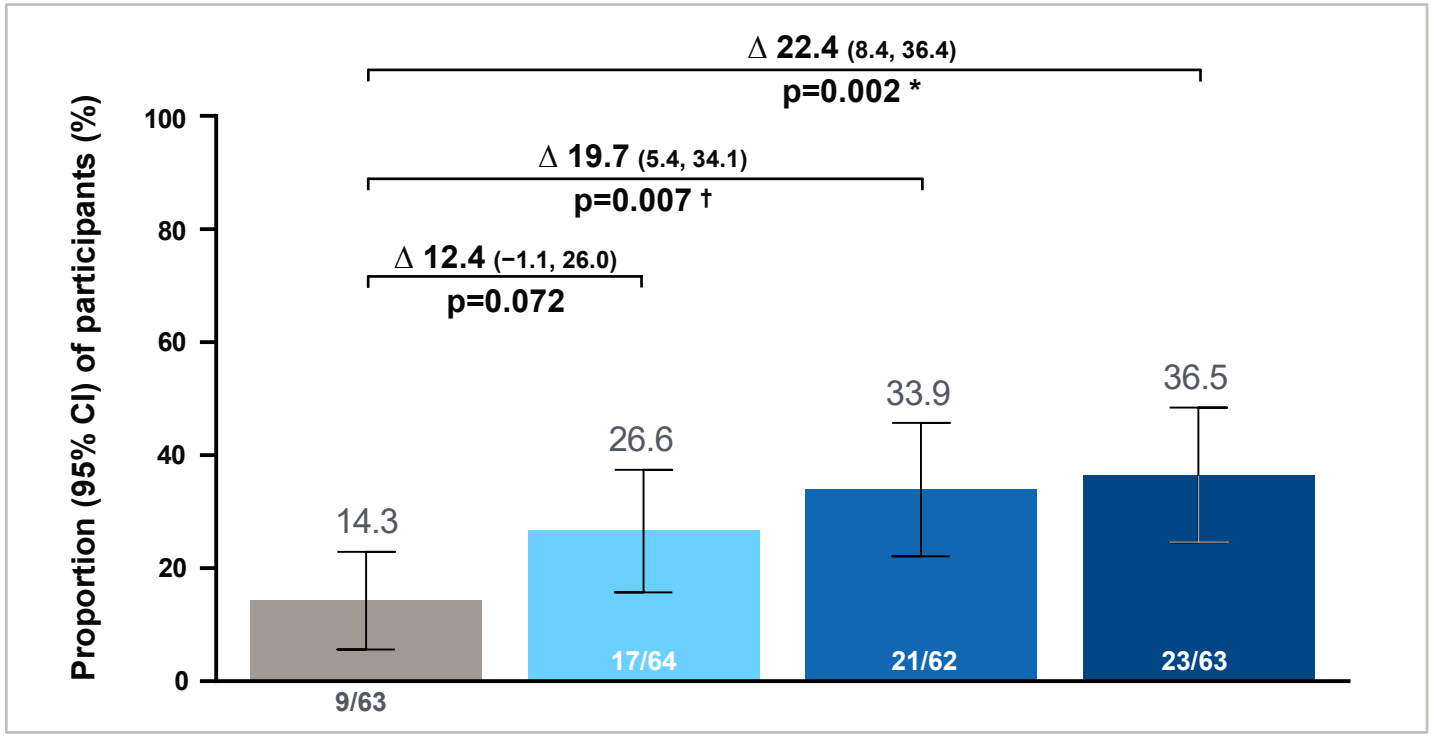
- Placebo
- Icotrokinra 100 mg qd
- Icotrokinra 200 mg qd
- Icotrokinra 400 mg qd

Symptomatic remission: stool frequency subscore of 0 or 1 and rectal bleeding subscore of 0

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopy subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders, as were participants who had missing data for the endpoint. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Protagonist Therapeutics

Endoscopic Improvement at Week 12



Placebo

Icotrokinra 100 mg qd

Icotrokinra 200 mg qd

Icotrokinra 400 mg qd

* Statistically significant based on testing procedure

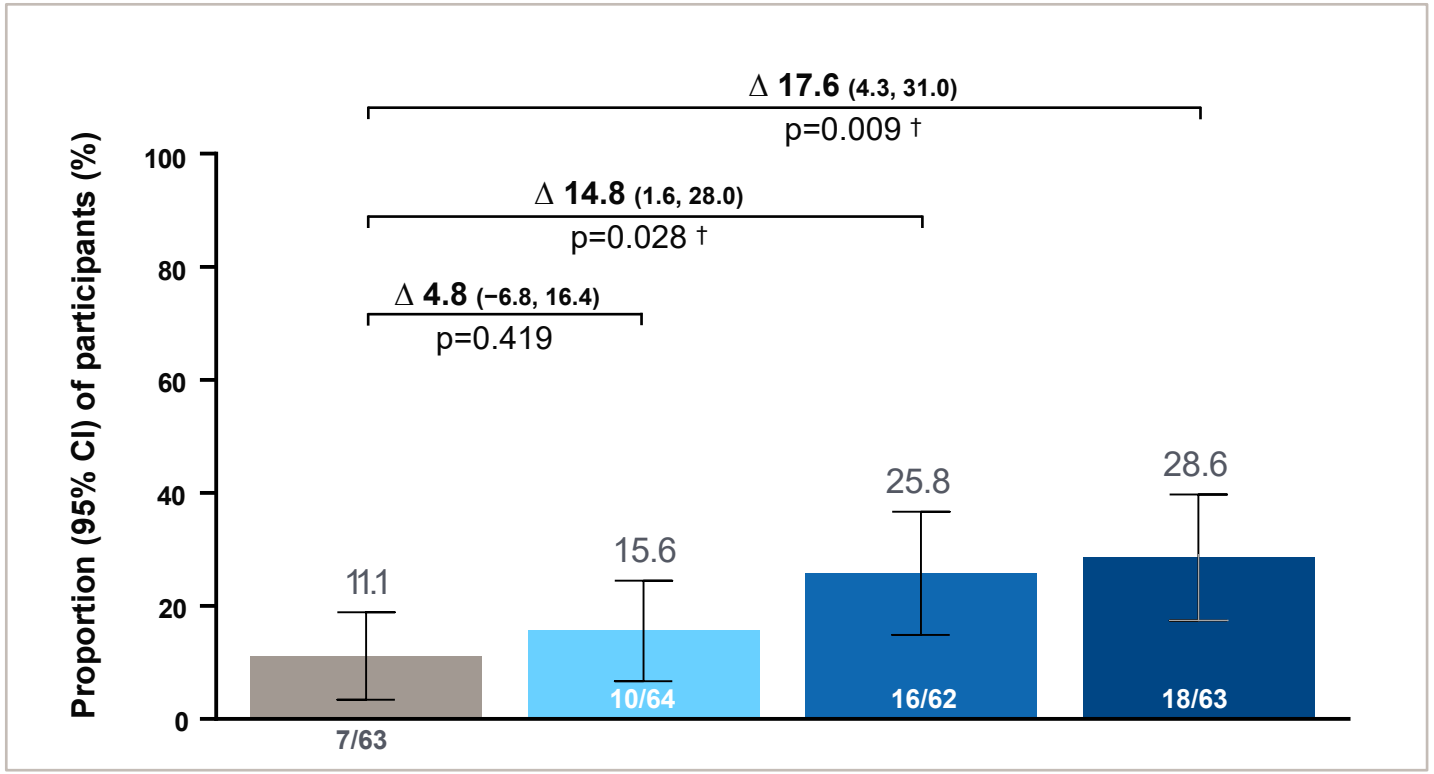
† Nominal p-value <0.05

Endoscopic improvement: Mayo endoscopy subscore of 0 or 1

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopy subscore (moderate [2] or severe [3]). Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders, as were participants who had missing data for the endpoint. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Protagonist Therapeutics

Histologic–Endoscopic Mucosal Improvement (HEMI) at Week 12



† Nominal p-value <0.05

Histologic-endoscopic mucosal improvement: histologic remission (absence of neutrophils from the mucosa in both lamina propria and epithelium, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system) AND endoscopic improvement (MES of 0 or 1)

Δ = adjusted treatment difference (95% confidence interval) and p-value vs placebo. Adjusted treatment differences, 95% CIs, and p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator, using stratification factors of BIO/JAKi/S1Pm-IR status (Yes or No) and Mayo endoscopy subscore (moderate [2] or severe [3]).
Participants with intercurrent events of ostomy or colectomy, prohibited changes in UC medication, or discontinuation of study intervention for any reason except those due to major disruptions (e.g., COVID-19 related reasons or regional crisis, excluding COVID-19 infection) were considered nonresponders, as were participants who had missing data for the endpoint. For participants discontinuing study intervention due to major disruptions, their observed values, if available, were used. After accounting for these scenarios, participants who were missing data necessary for calculation of the outcome measure at the assessment timepoint were considered not to have achieved that endpoint.

Protagonist Therapeutics

Summary of Adverse Events Through Week 12

	Placebo	Icotrokinra 100 mg QD	Icotrokinra 200 mg QD	Icotrokinra 400 mg QD
Safety analysis set, N	63	64	62	63
Average duration of follow-up, weeks	11.7	12.0	12.0	11.9
Average duration of treatment, weeks	11.2	11.8	11.7	11.6
Deaths, n (%)	0	0	0	0
Participants with 1 or more, n (%)				
AEs	32 (50.8%)	32 (50.0%)	28 (45.2%)	29 (46.0%)
Serious AEs	3 (4.8%)	0	2 (3.2%)	1 (1.6%)
AEs leading to discontinuation of study agent	5 (7.9%)	0	4 (6.5%)	1 (1.6%)
Infections[a]	12 (19.0%)	11 (17.2%)	16 (25.8%)	12 (19.0%)
Serious infections[a]	1 (1.6%)	0	0	0
Most common AEs (frequency ≥5% in any group), n (%)				
Worsening of ulcerative colitis	5 (7.9%)	3 (4.7%)	5 (8.1%)	3 (4.8%)
Headache	1 (1.6%)	5 (7.8%)	2 (3.2%)	4 (6.3%)
Upper respiratory tract infection	1 (1.6%)	4 (6.3%)	3 (4.8%)	4 (6.3%)
Nasopharyngitis	1 (1.6%)	3 (4.7%)	0	6 (9.5%)
COVID-19	0	0	4 (6.5%)	0

Protagonist Therapeutics

a. Infections were defined as any adverse event coded to the MedDRA system organ class 'Infections and infestations'.

Conclusions

- In adults with moderately to severely active ulcerative colitis, all tested doses of once-daily oral icotrokinra achieved the primary endpoint of clinical response at Week 12
- At Week 12, icotrokinra 400 mg QD was superior to placebo for clinical remission, symptomatic remission, and endoscopic improvement with clinically meaningful differences observed for histologic–endoscopic mucosal improvement (HEMI)
- Icotrokinra was well tolerated: the proportions of participants experiencing AEs through Week 12 were similar for placebo and all icotrokinra doses
- Icotrokinra, the first-in-class targeted oral peptide that selectively blocks the IL-23 receptor, has potential to offer therapeutic benefit with a favorable safety profile in a once-daily oral treatment for ulcerative colitis

Icotrokinra Phase 2 ANTHEM-UC Study[1]

Key Findings

- Positive outcome showing potential to transform UC treatment paradigm
- At week 12, the highest dose achieved
  - 1° endpoint: **Clinical response = 63.5%**
  - 2° endpoint: **Clinical remission = 30.2%**
  - Clinical remission and response rates continued to improve through week 28
- All 3 doses met the primary endpoint of clinical response at week 12, with a favorable safety profile
- Clinically meaningful differences versus placebo in key secondary endpoints of clinical remission, symptomatic remission, and endoscopic improvement at week 12
- **Next steps:** More advanced clinical studies in ulcerative colitis and Crohn's disease

Icotrokinra has the potential to transform the treatment landscape in UC through its distinctive profile of efficacy, safety, tolerability, and convenience of a once-daily oral treatment.

Protagonist Therapeutics

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.

Next Steps:

Icotrokinra Phase 3 Ulcerative Colitis and Phase 2b/3 Crohn's Disease Clinical Studies Update

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

Potential registration-enabling, phase 3 studies underway in participants with moderately to severely active ulcerative colitis and Crohn's disease

[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 or 1.
[b]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.
[c]Clinical remission is defined as CDAI score <150. CDAI scores range from 0 to approximately 600. Higher score indicates higher disease activity.
[d]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

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

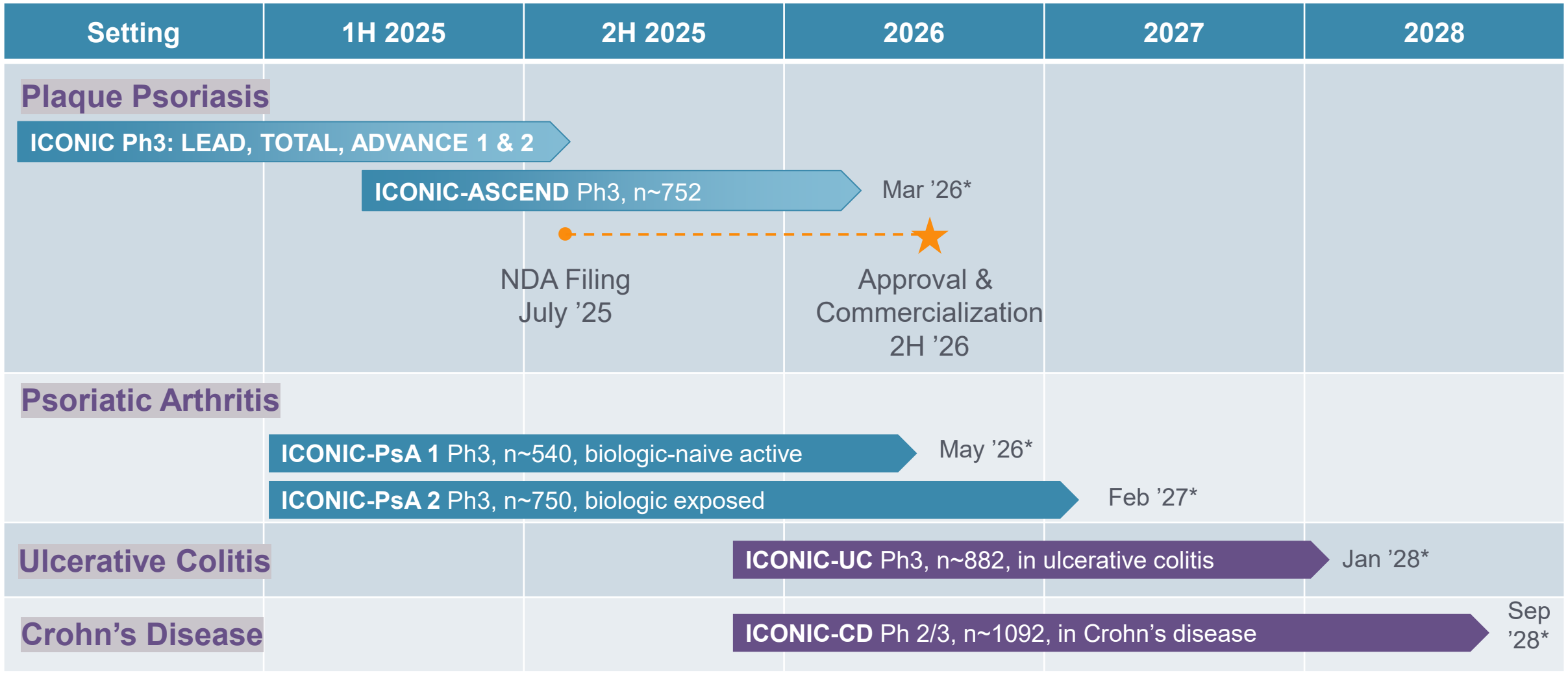
Ulcerative Colitis (UC)

- 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

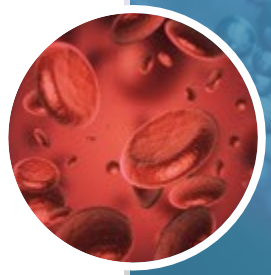
Addressing Unmet Needs in Polycythemia Vera

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

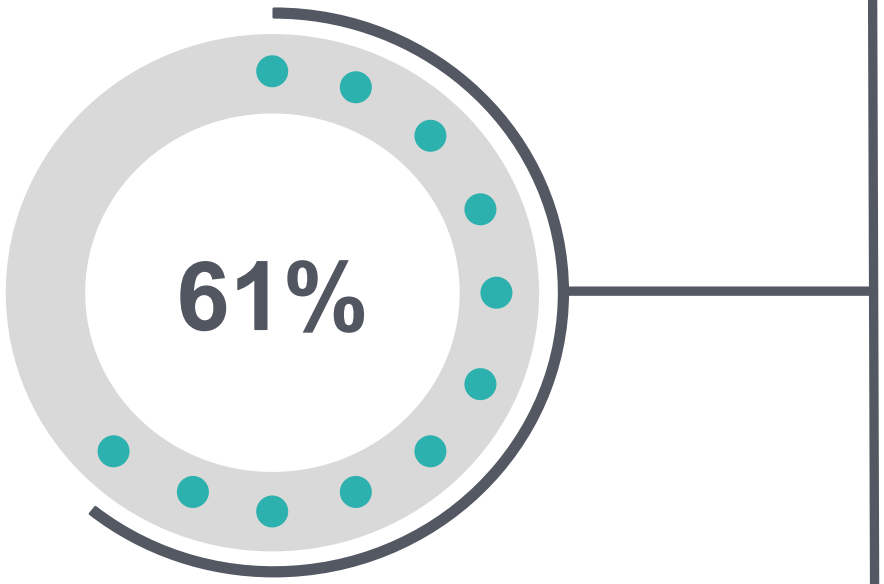
Occurrence of thrombotic events following treatment initiation can be an indicator of the ineffectiveness of the treatment – an example of a sub-optimally controlled PV patient

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

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

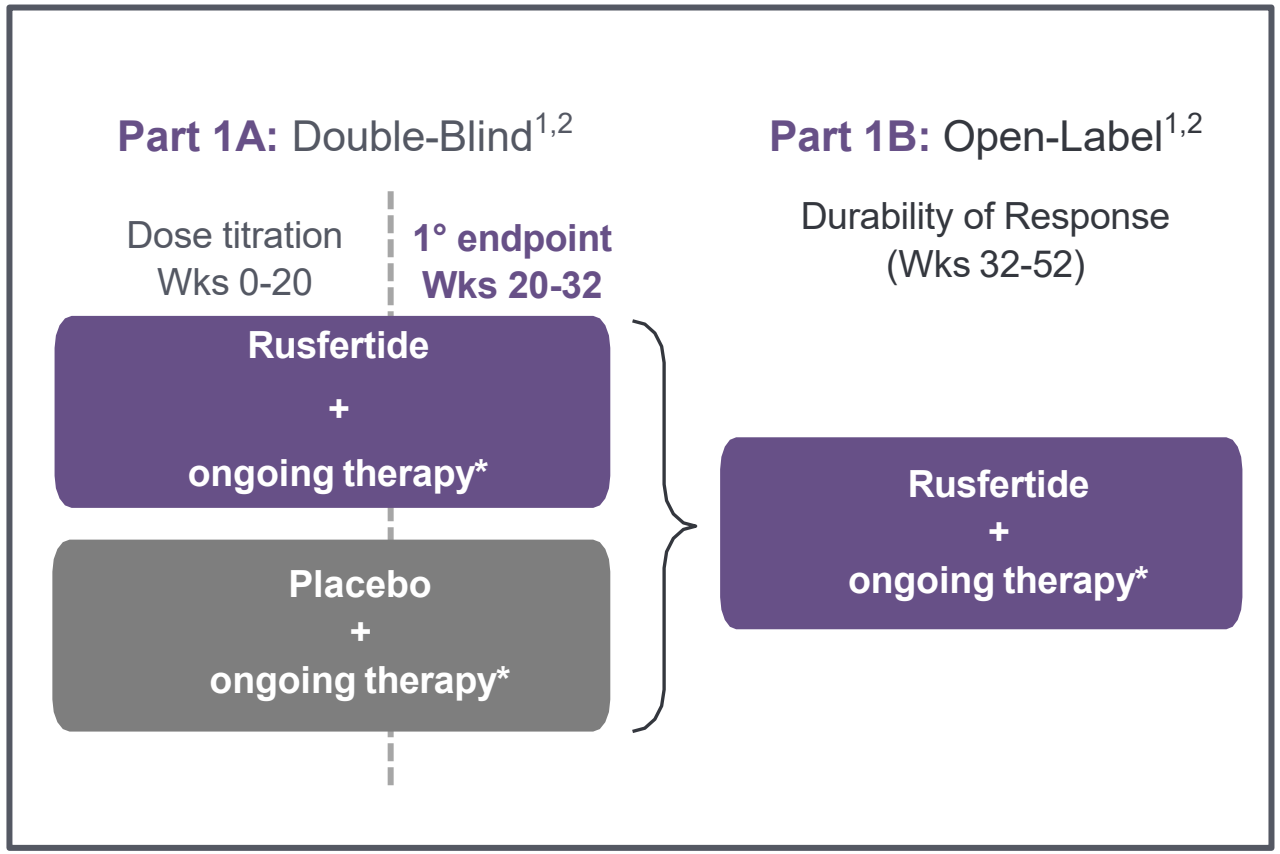
ASCO 2025 Plenary Session

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

VERIFY is a **global, randomized, double-blind phase 3 study** investigating rusfertide or placebo with current standard-of-care therapy in patients with PV

VERIFY met its prespecified primary endpoint (response) **and all four key secondary endpoints**, including reduction in phlebotomy and improvement in symptoms (assessed by PRO measures) vs. placebo

Rusfertide was well tolerated and had a safety profile that was consistent with prior observations in phase 2 studies of patients with PV, including REVIVE

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.

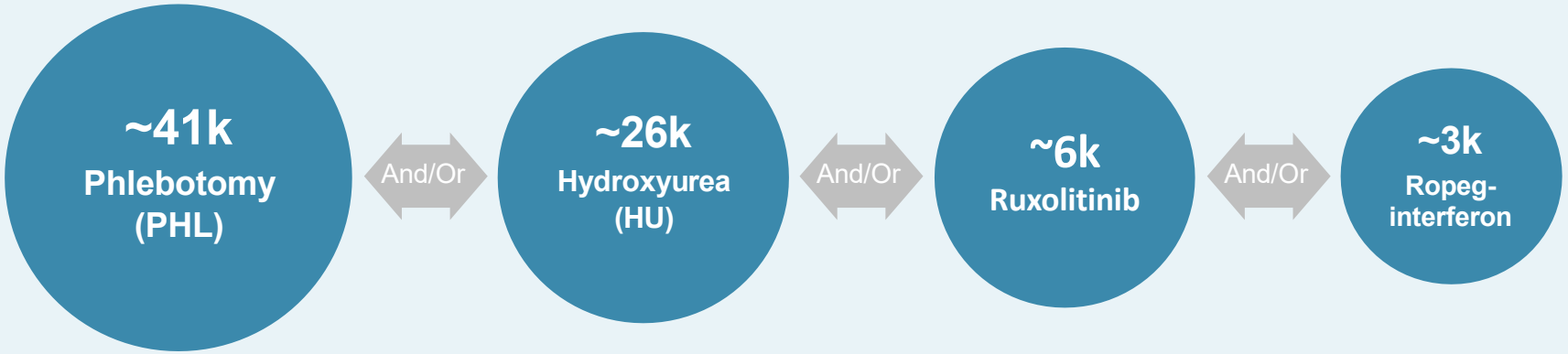
Polycythemia Vera: Prevalence, Treatment Paradigm and Unmet Need

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]



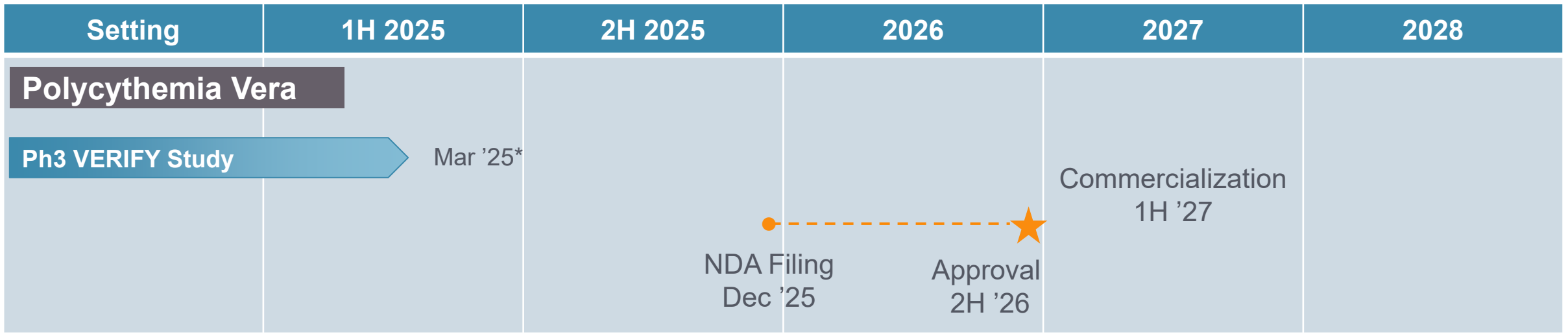
- Unmet need exists at each step of the treatment landscape
  - **~78% with uncontrolled Hct<45%**[3]
- **Rusfertide expected to be used at each step**[1]

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

Rusfertide for PV: Clinical Development, Approval and Commercialization Timelines



* Primary Completion Date

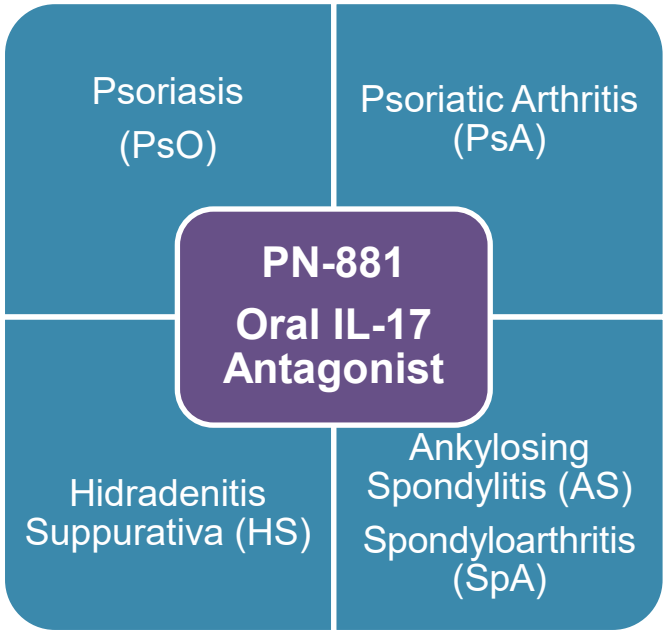
Protagonist Therapeutics

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



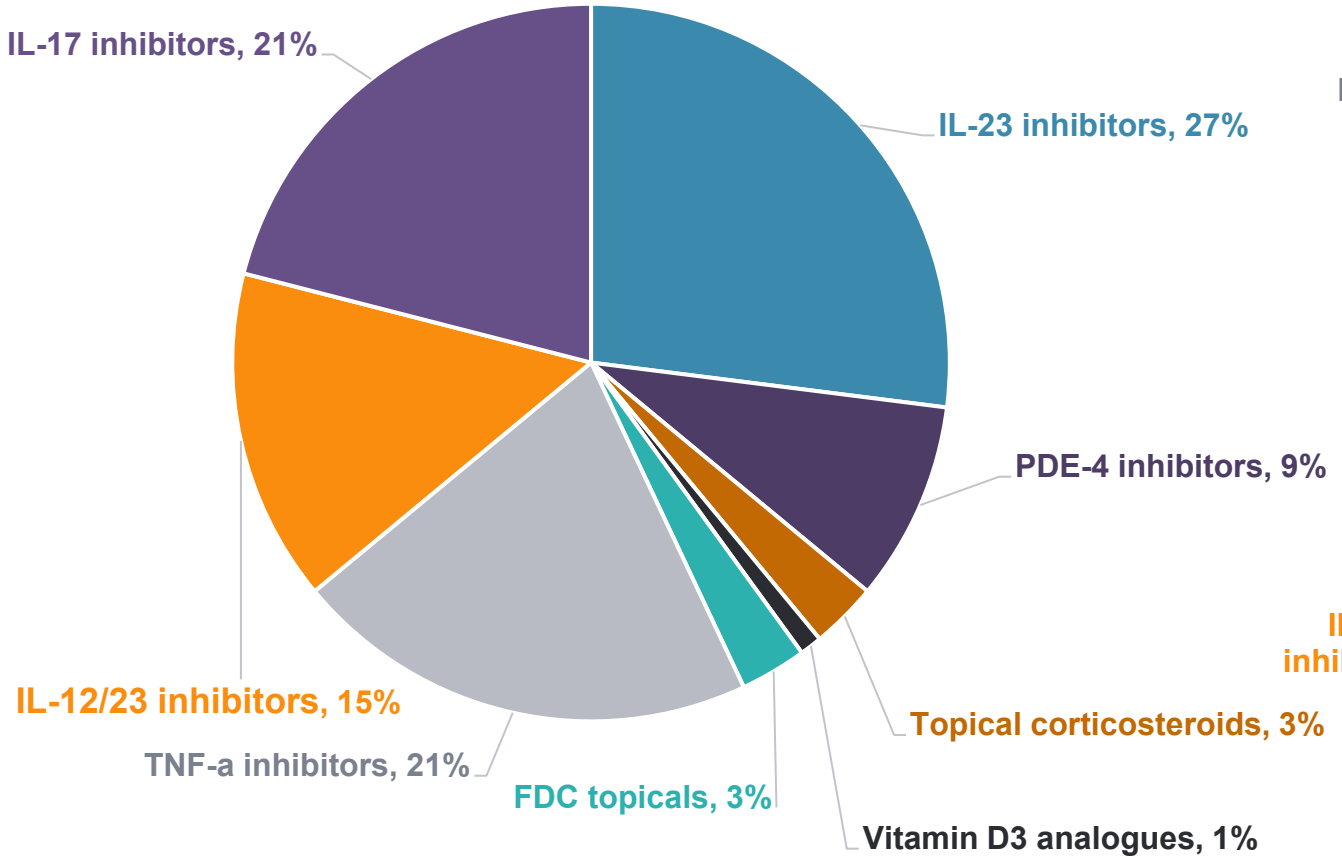
1. Psoriasis Disease Landscape and Forecast (Clarivate, 2023);
2. No approved oral IL-17 antagonists. Approved IL-17 mAbs: COSENTYX (secukinumab), TALTZ (ixekizumab), and BIMZELX (bimekizumab)
3. Blockade of both IL-17A and IL-17F leads to greater efficacy. Reich et al., N Engl J Med 2021;385:142-52.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

Protagonist Therapeutics

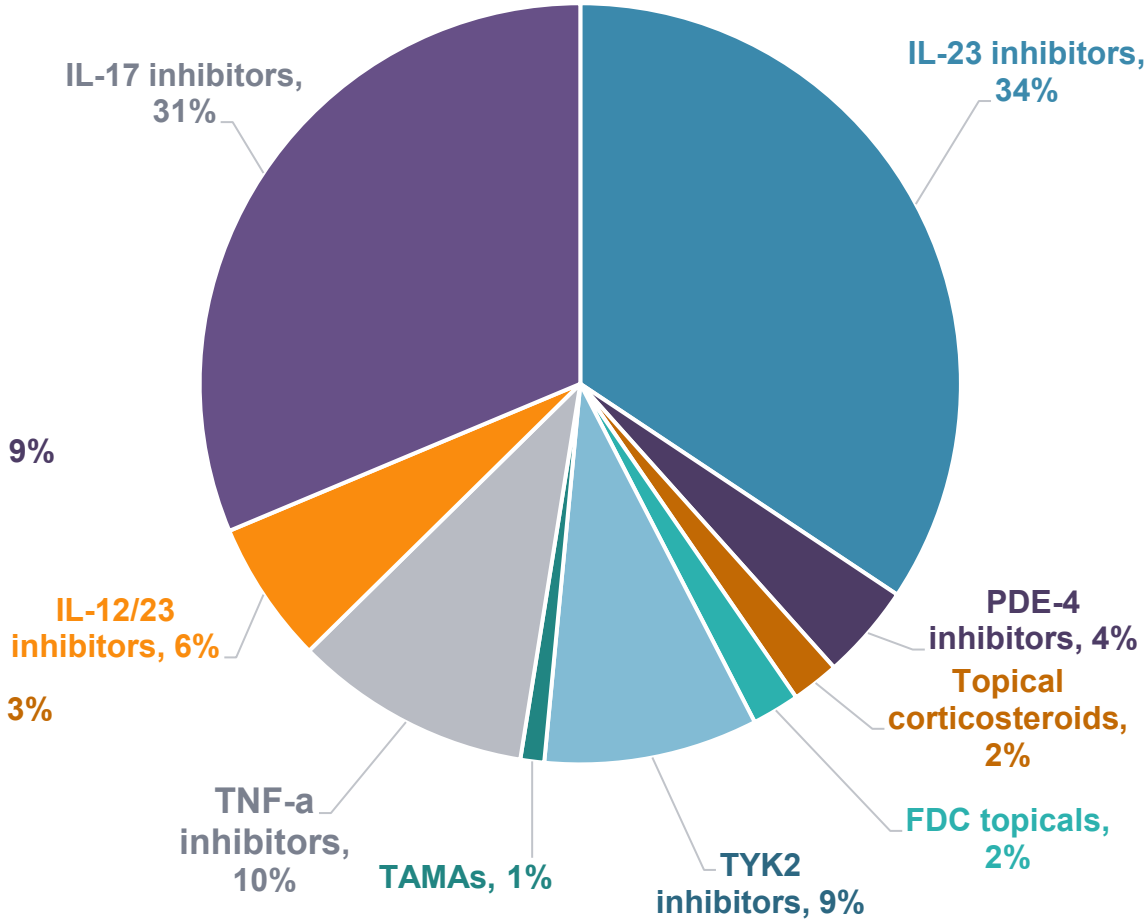
Psoriasis Market Share by Drug Class

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

2021 DISTRIBUTION
Market Size: $21.7B



2031 DISTRIBUTION
Market Size: $30.1B

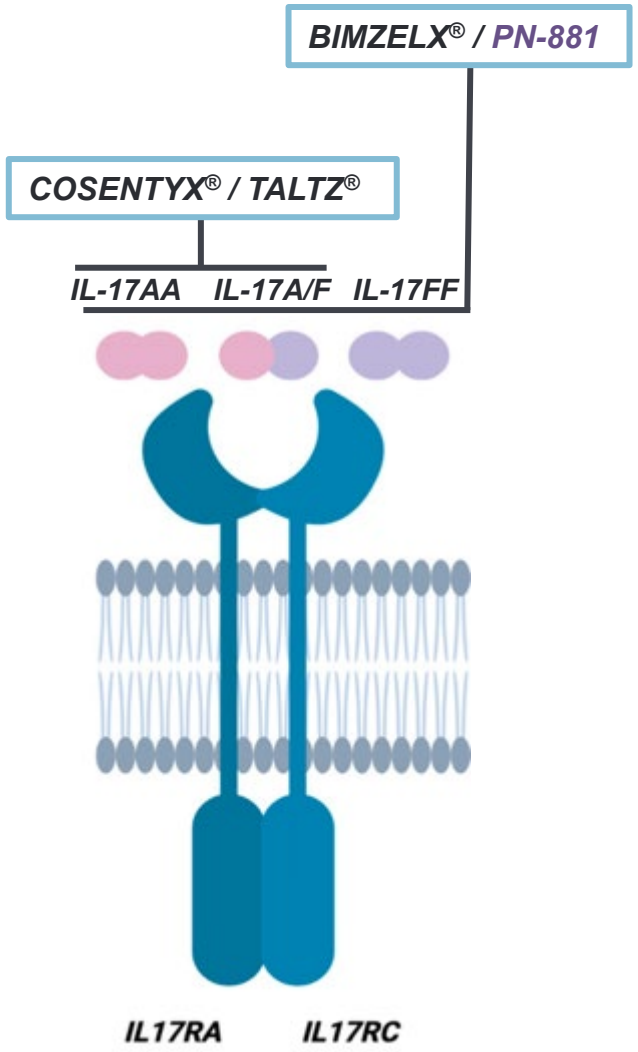


Protagonist Therapeutics

Psoriasis Disease Landscape and Forecast (Clarivate, 2023).

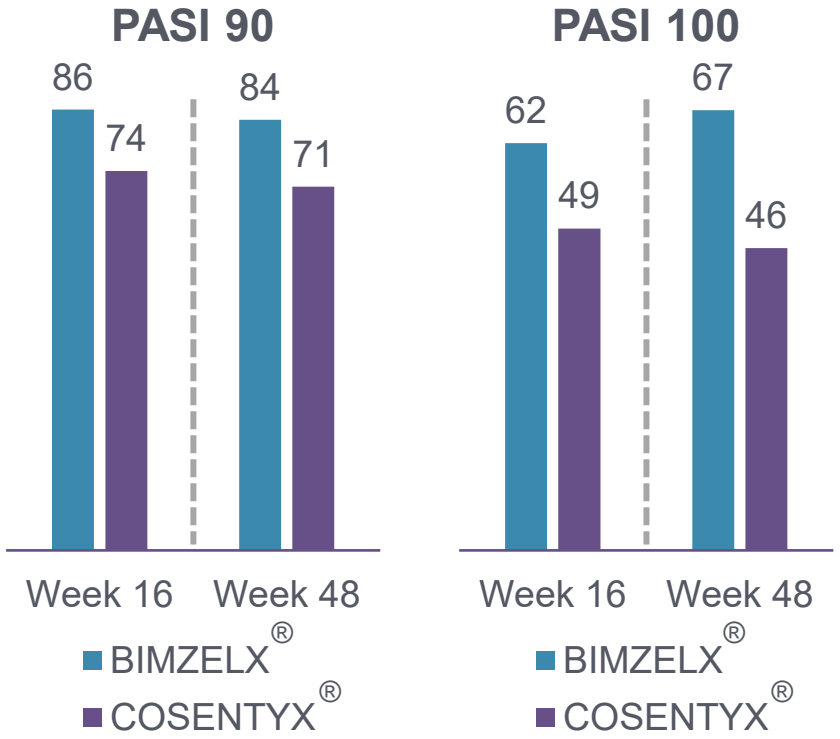
IL-17 Receptor Activated by Three Dimeric Forms of IL-17: IL-17AA, AF, and FF[1]

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

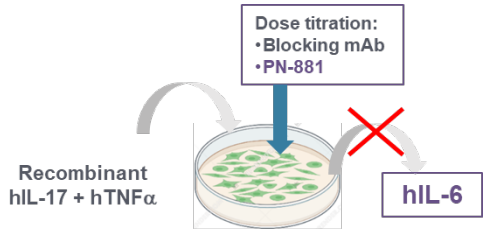
Attribute	Criteria
Potency	• **Sub-nM potency *vs.* IL-17 AA** • **Blocks all dimeric forms of IL-17: AA, AF, FF**
Stability	• Stable in simulated gastric and intestinal fluids • Stable in serum with $t_{1/2}$ >24 hr • Metabolic stability • Thermostability
PK	• Oral exposure and half-life in rodent and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

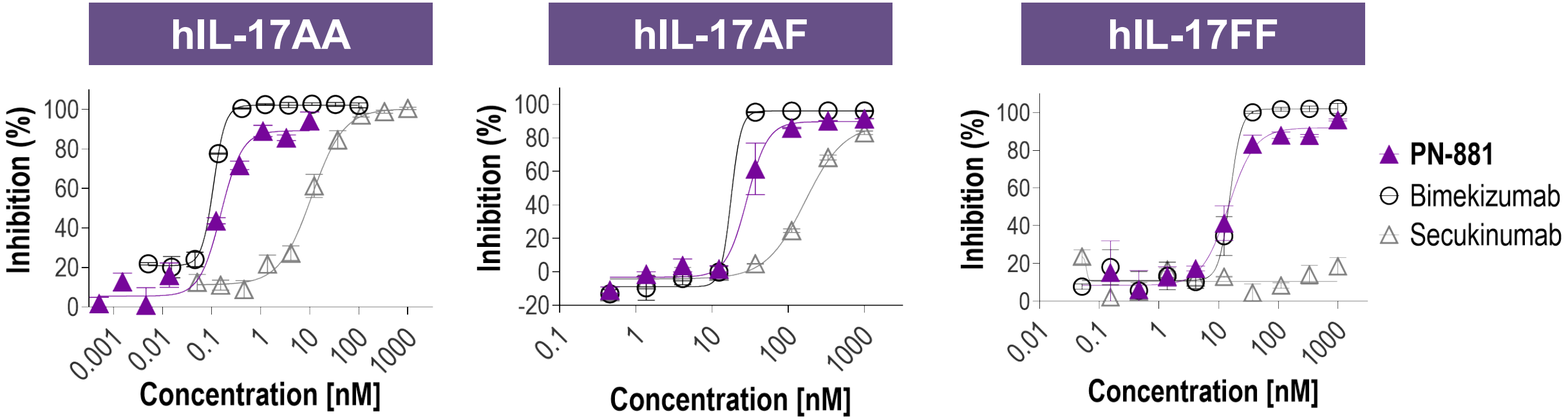
Protagonist Therapeutics

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

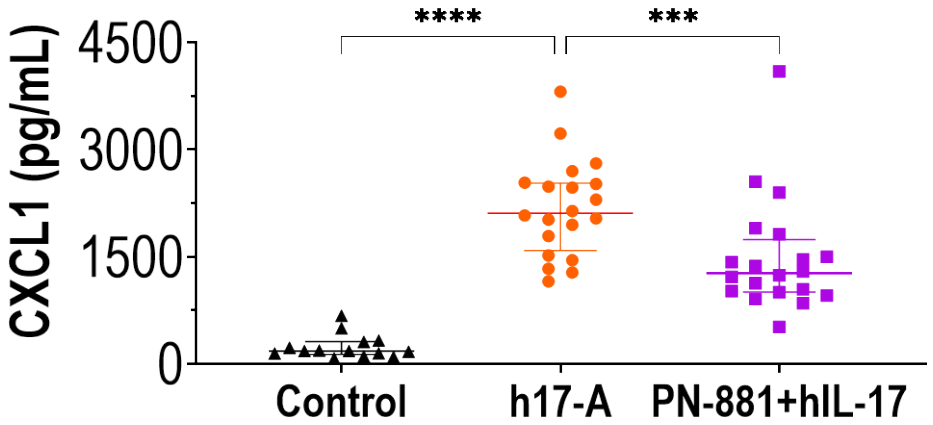
Oral PN-881 Neutralizes Human IL-17 in Mouse IL-17 Challenge PD Model[1]

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

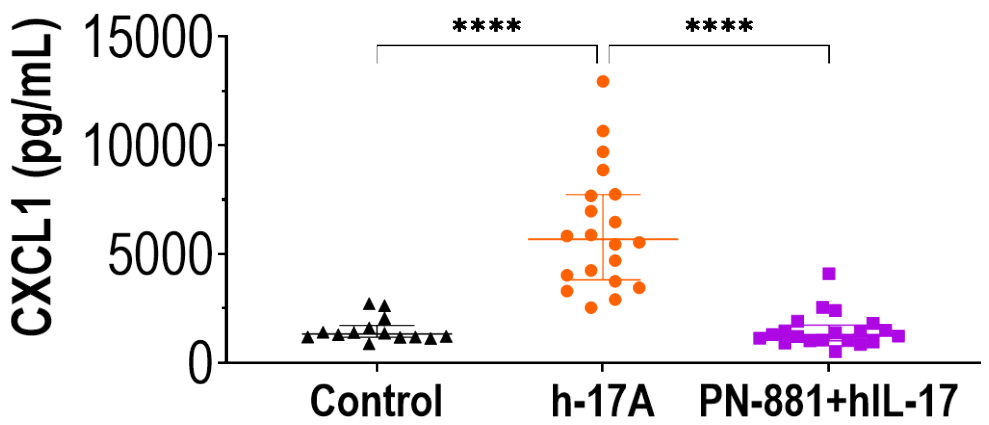
Treatment Groups:
a) Vehicle control
b) IL-17 alone
c) PN-881 (PO, QD)

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

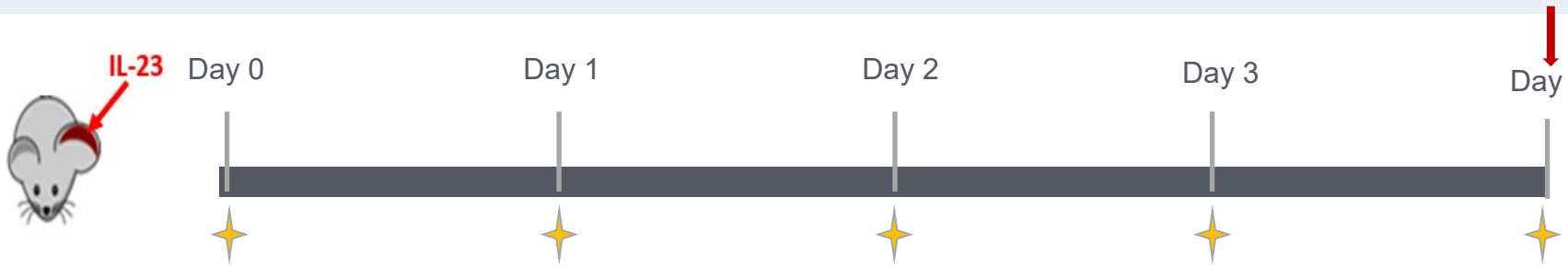
- Human IL-17 s.c. challenge induced systemic and skin production of CXCL1
- Oral administration of **PN-881** significantly reduced CXCL1 responses in serum and skin

Protagonist Therapeutics

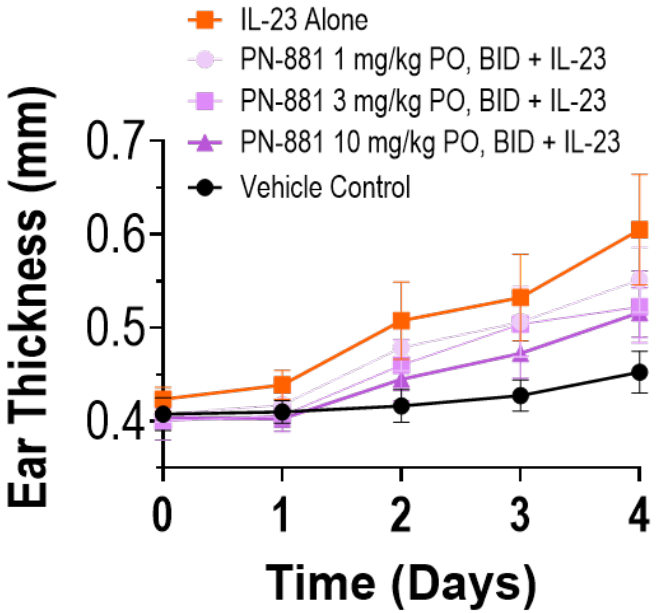
1. Manrique M, et al. Presented at the European Academy for Dermatology and Venereology (EADV) Congress. September 17-20, 2025, Paris, France.

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

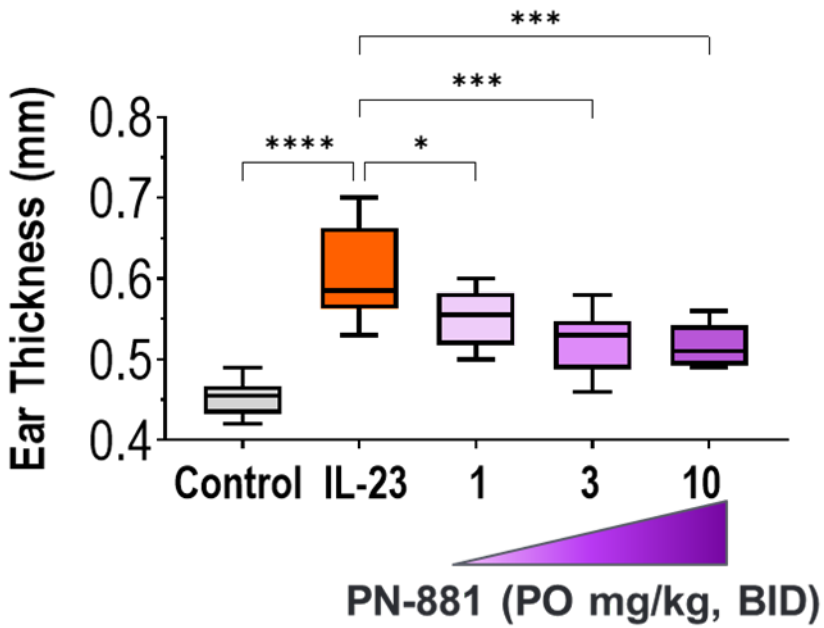
PN-881 Significantly Reduces IL-23-induced Ear Thickness After Oral Administration



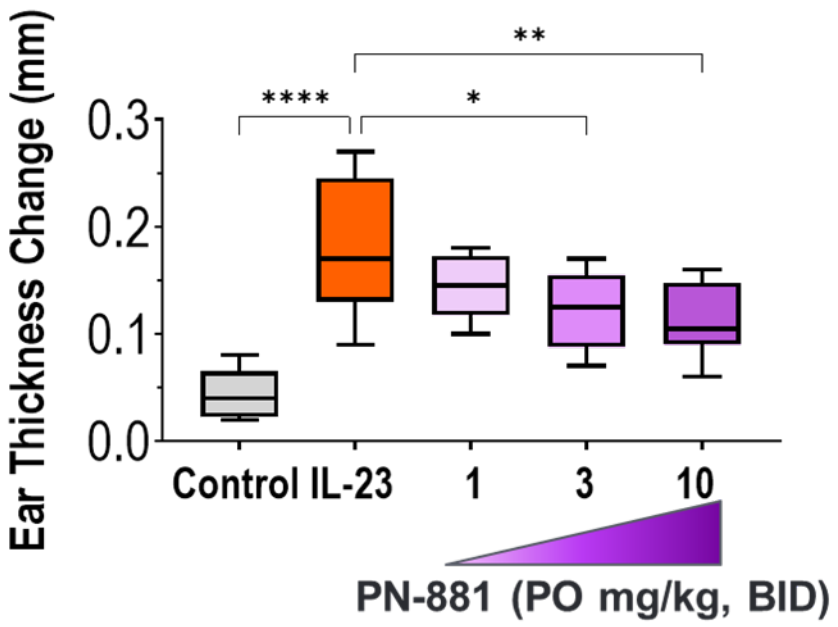
Ear Thickness Over Time



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

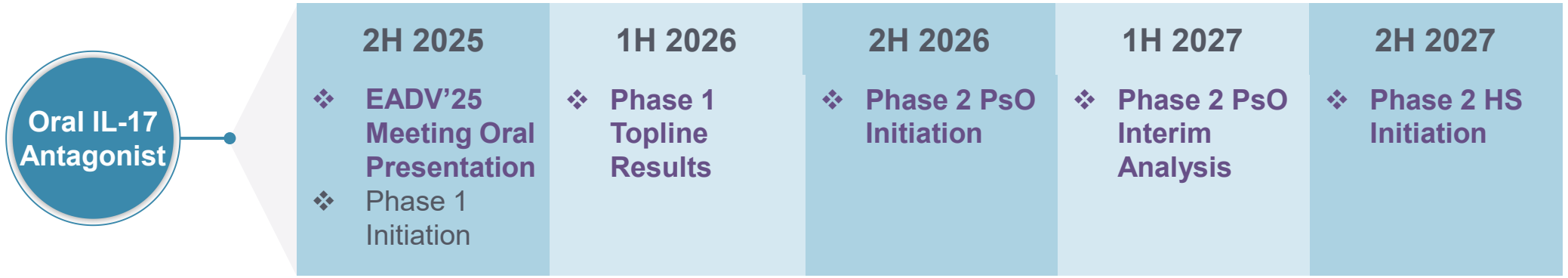
Primary Completion Date: Jun '26

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



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

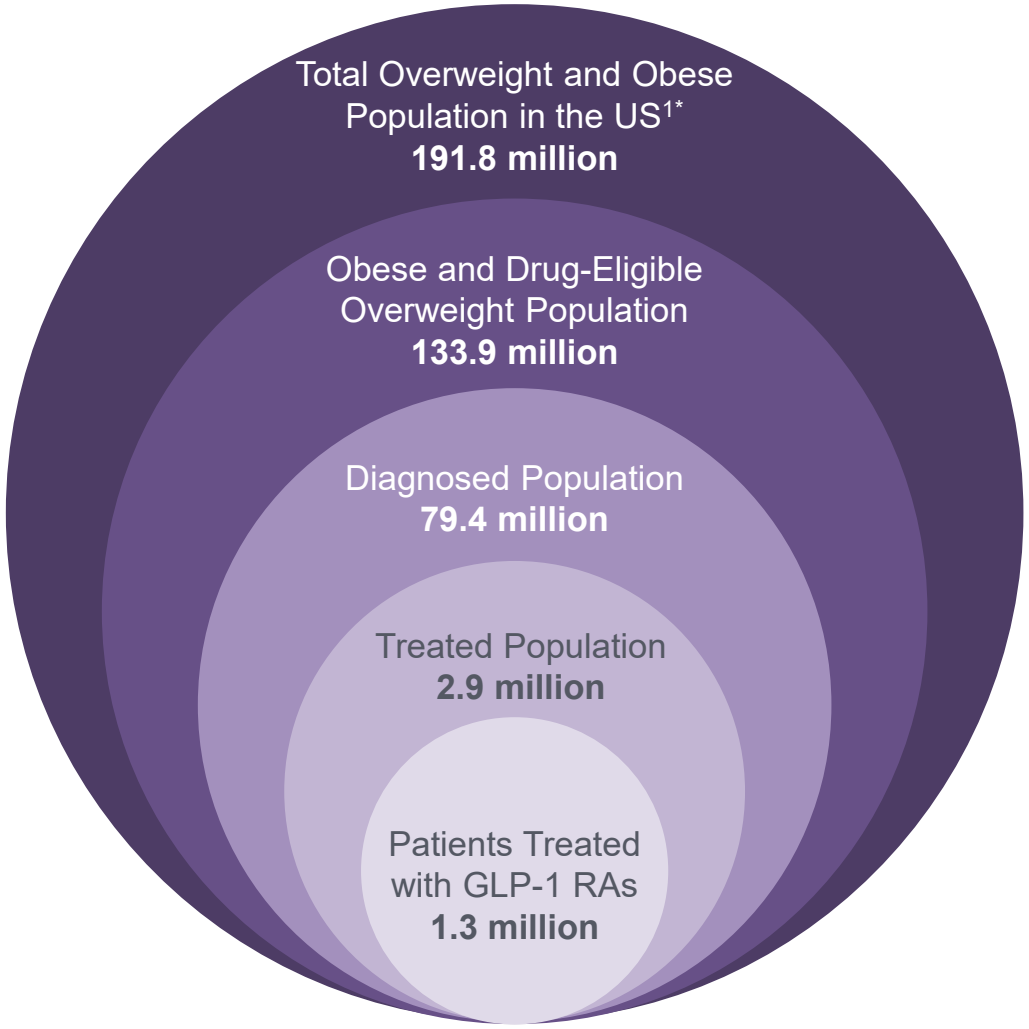
Protagonist Therapeutics

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]

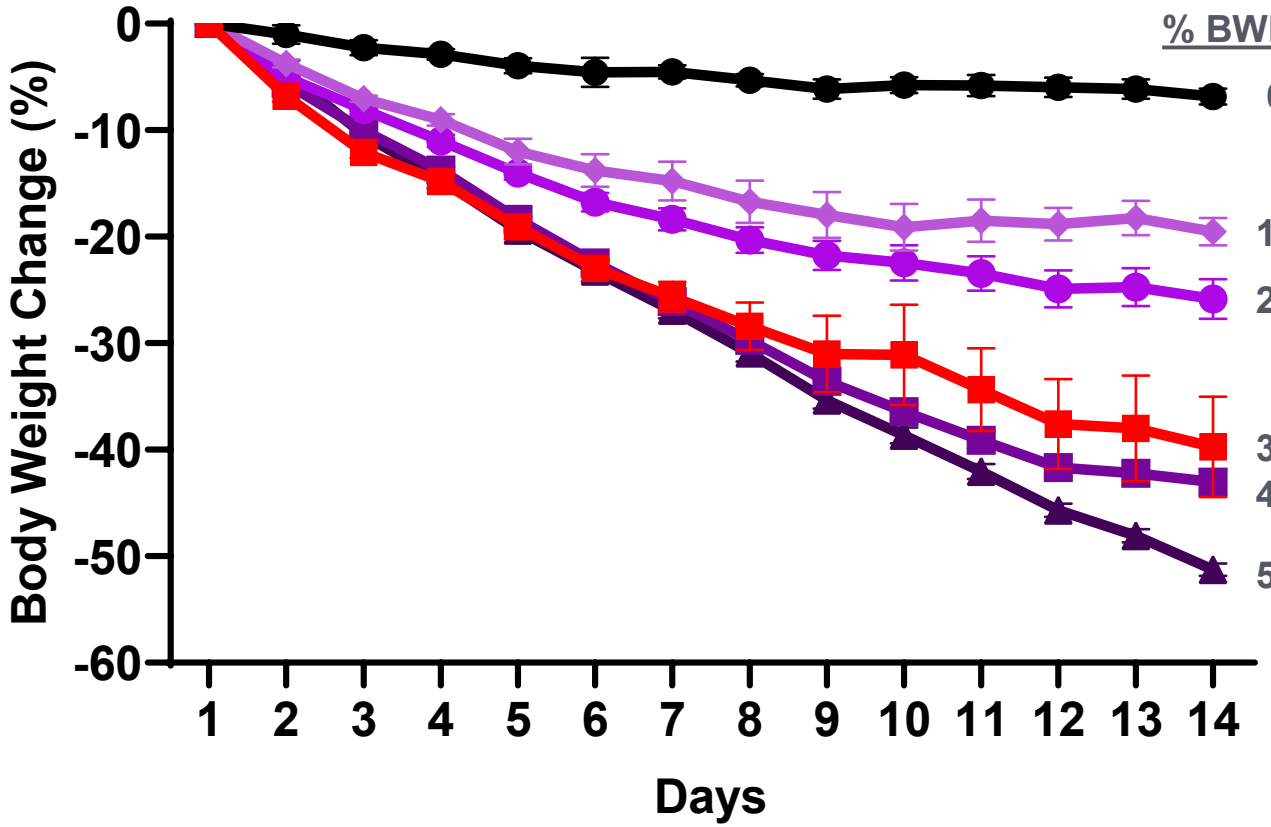
Protagonist Therapeutics

[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)

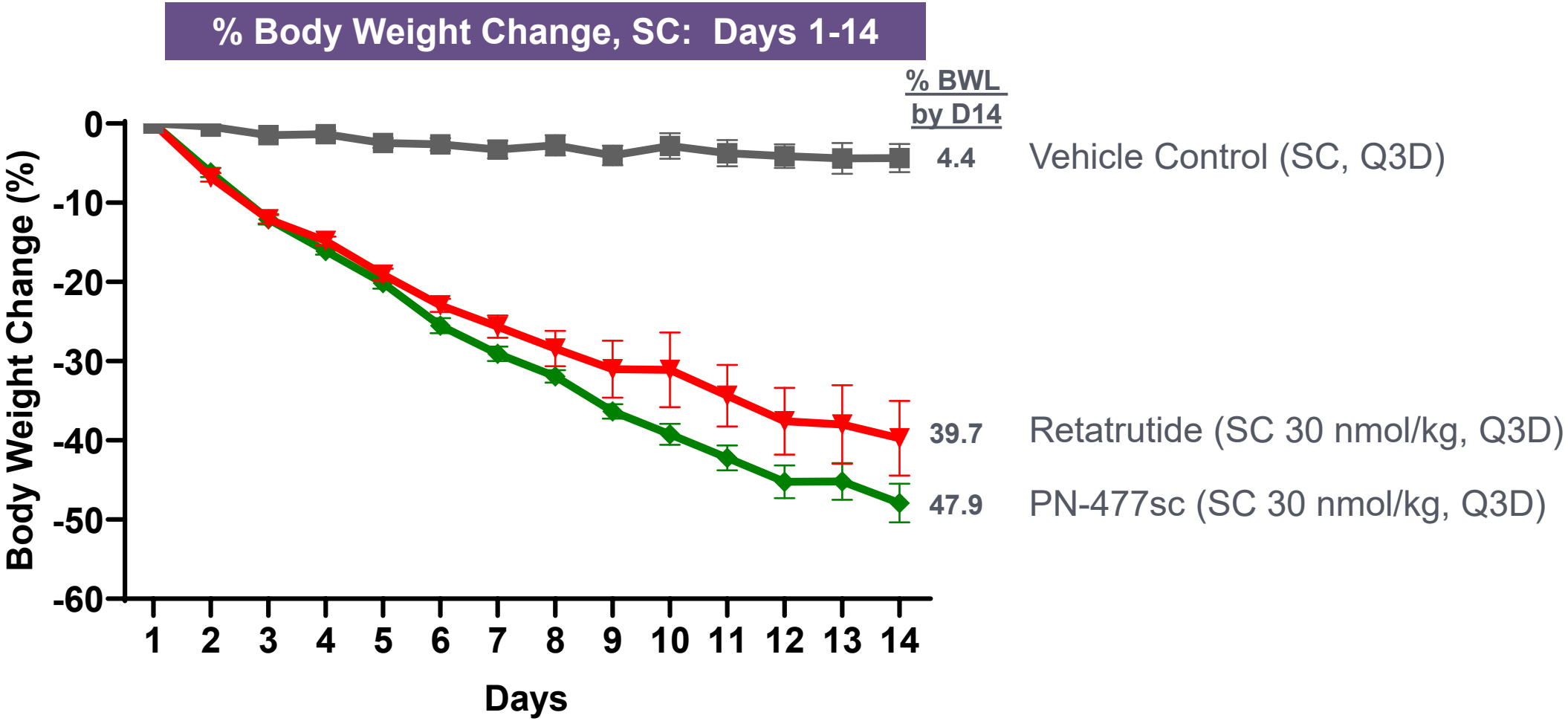
* Retatrutide SC 30 nmol/kg dose is the highest dose reported for DIO mouse efficacy study
(Cell Metabolism 34, 1234–1247, September 6, 2022)

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



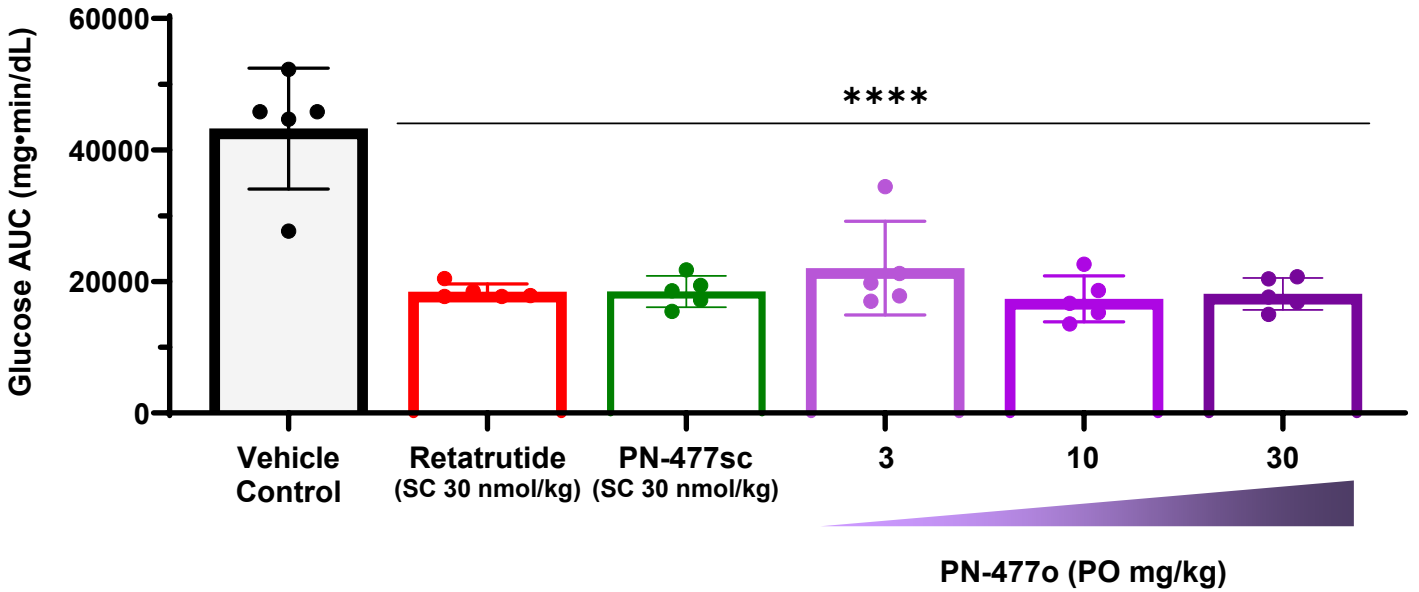
Protagonist Therapeutics

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

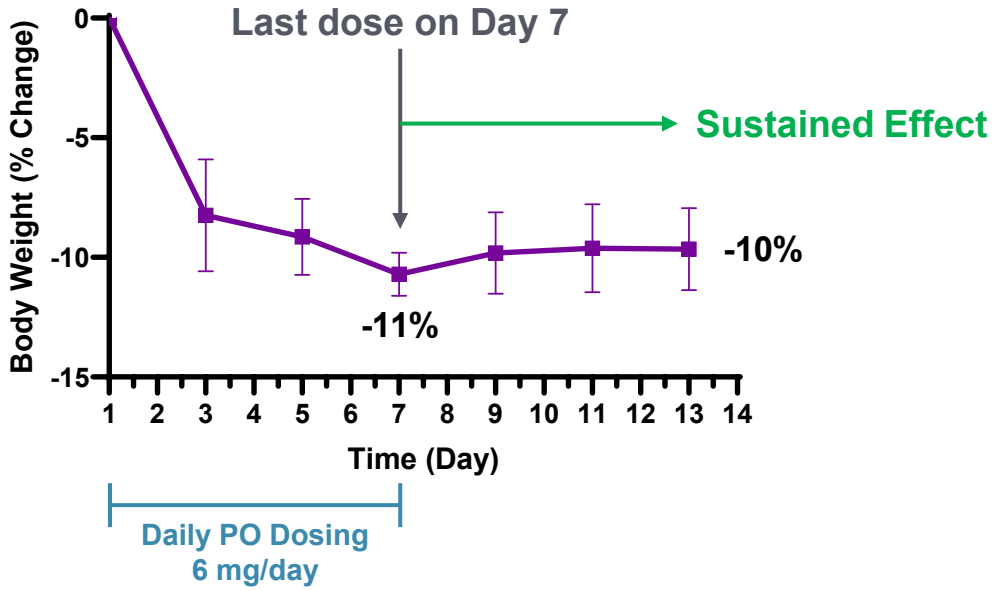
Protagonist Therapeutics

****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

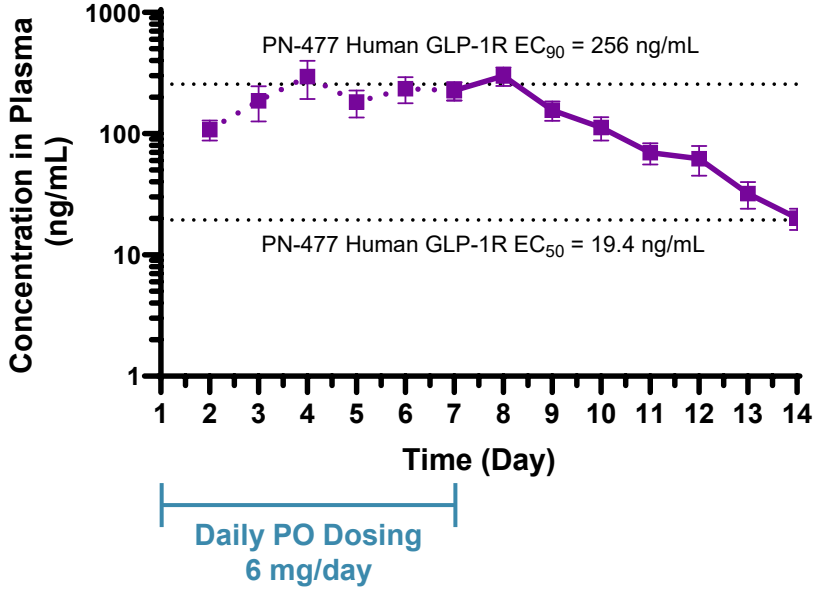
11% BW Loss by Day 7 in Cynomolgus Monkeys after 7-Day Oral Dosing of PN-477o

Weight Loss Sustained for 6 Days After Last Dose

Cyno % BW Change, PO



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



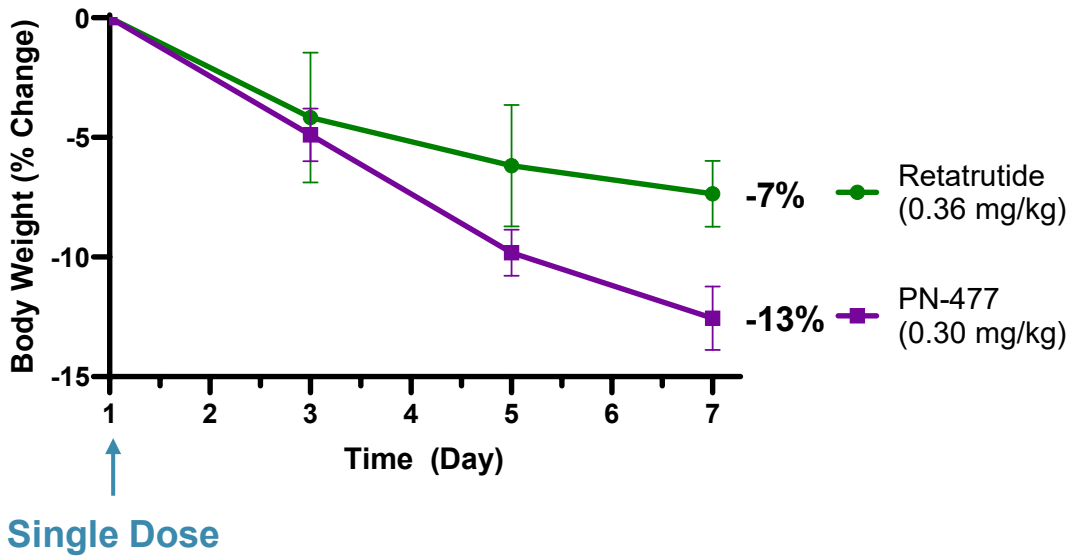
- PN-477o PK profile suggests once daily human dosing
- Body weight loss was sustained for 6 days post-last dose

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

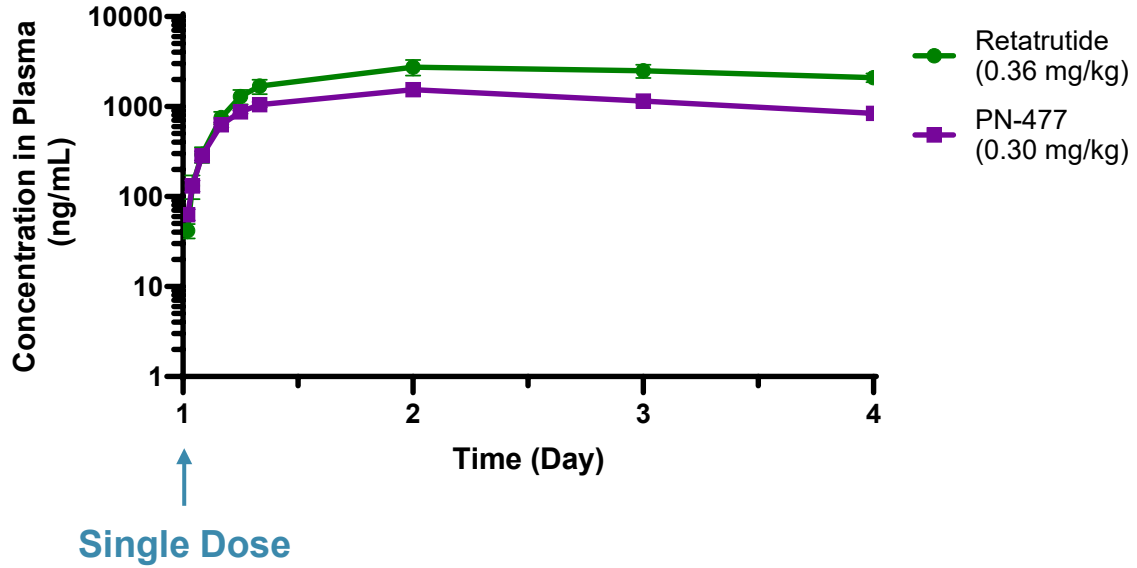
13% BW Loss by Day 7 in Normal Monkeys after Single SC Dose of PN-477

PN-477 Vs. Retatrutide

Cyno % BW Change, SC



Cyno PK, SC



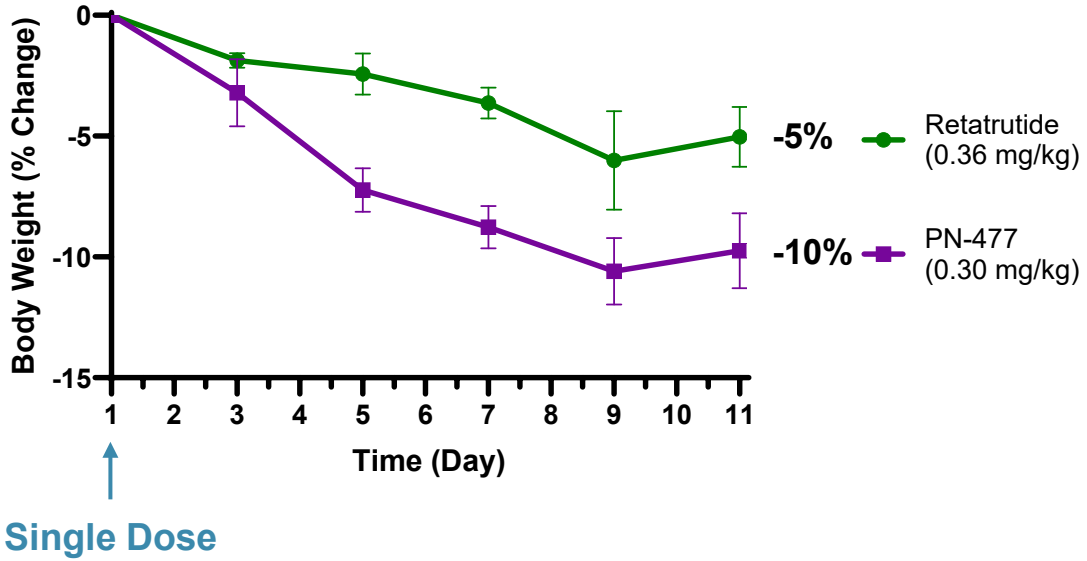
PN-477sc PK profile suggests once weekly human dosing

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

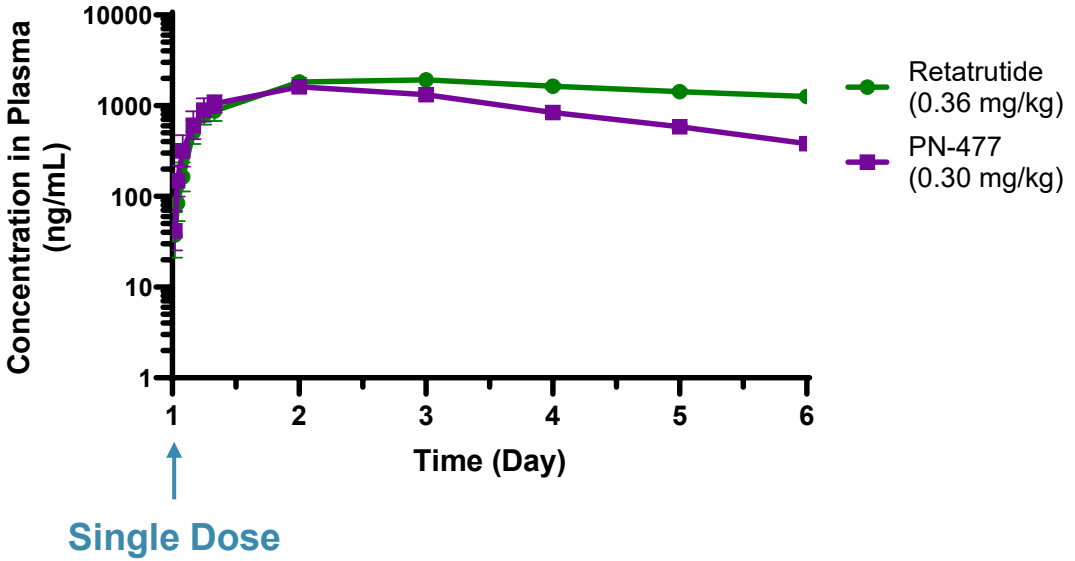
10% BW Loss by Day 11 in Normal Beagle Dogs after Single SC Dose of PN-477

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

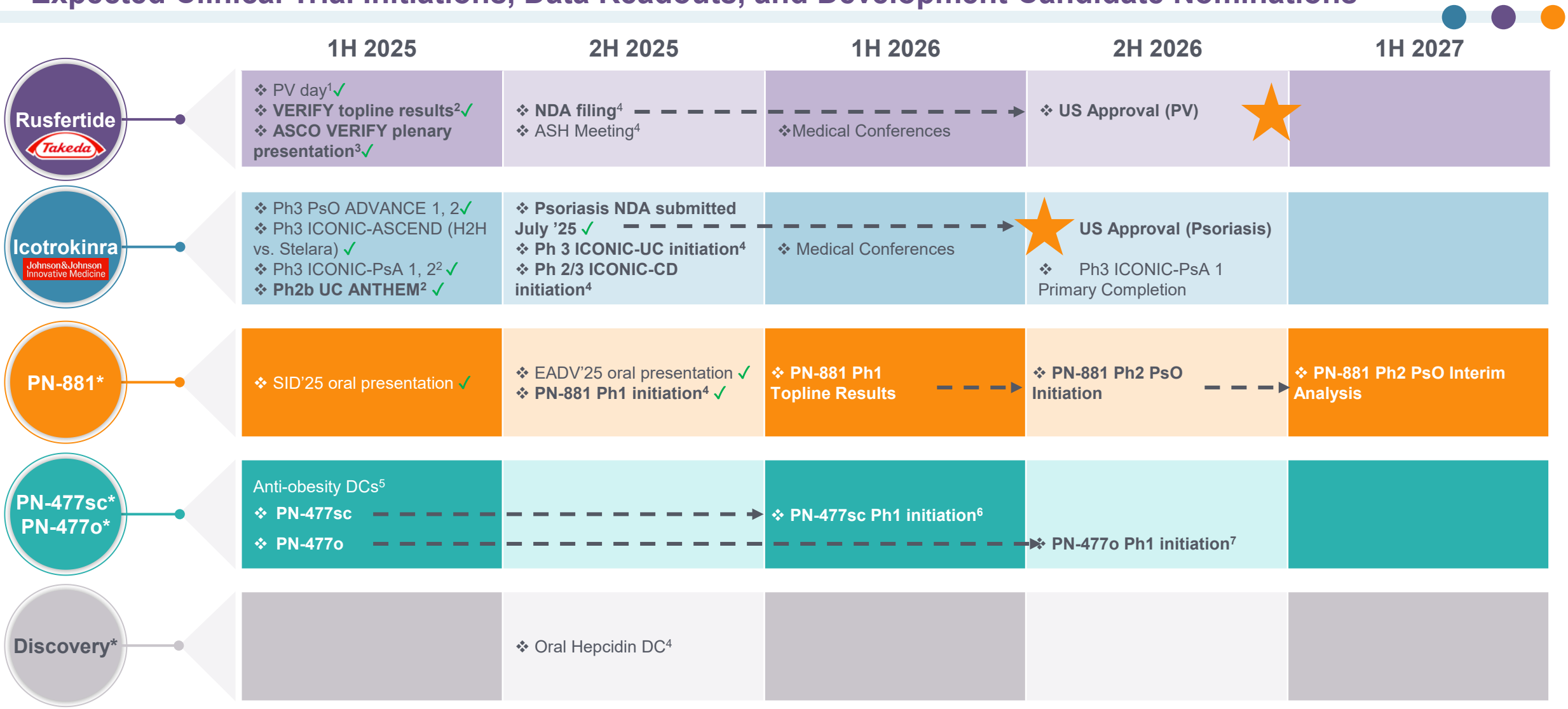
PN-477: A Potential Best-in-Class Triple Agonist Anti-Obesity Peptide Development Candidate with Convenience of Once-Daily Oral and Once-Weekly SC Dosing

- 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

Protagonist Therapeutics

Major Upcoming Catalysts in 2H 2025 Through 1H 2027

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



Protagonist Therapeutics

*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

Protagonist Therapeutics

Thank you