Protagonist Therapeutics

COMPANY OVERVIEW

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President & CEO

July 21, 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 IL-17 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) and rusfertide clinical results, 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

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

Oral Hepcidin
Program
Hematology

Preclinical

PN-477o
PN-477sc
Triple Agonist
Anti-Obesity
DC*

IND-Enabling

PN-881
Oral
IL-17 Antagonist

Ph 1 initiation ~Q4 '25

Rusfertide
SC Weekly Hepcidin Mimetic
PV, Ph3
Takeda

NDA filing ~EOY '25

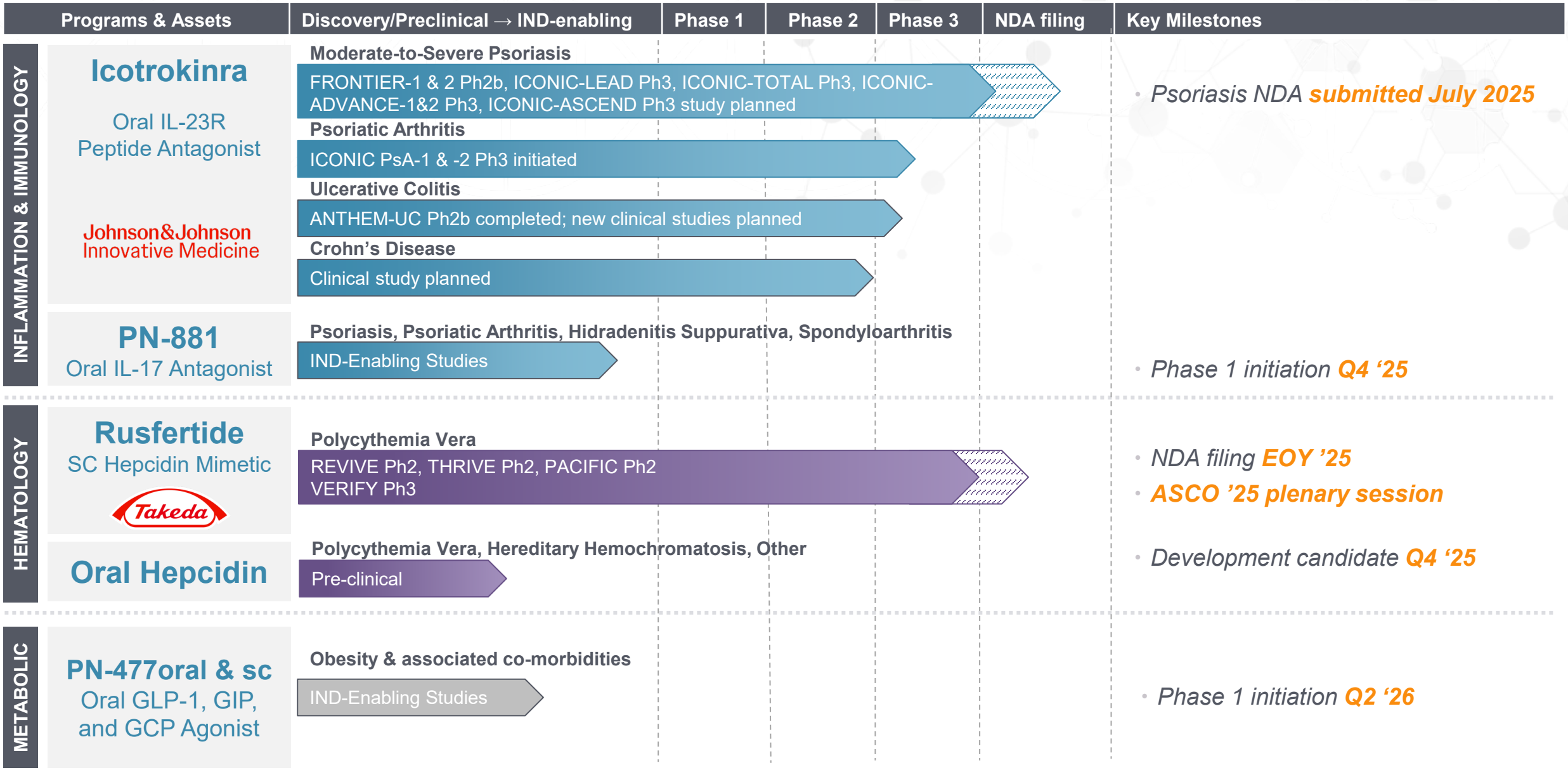
Icotrokinra
Oral IL-23r Antagonist
Psoriasis**, Ph3
Johnson&Johnson Innovative Medicine

Psoriasis NDA Submitted July 2025

Protagonist Therapeutics

* Development candidate (DC); Ready for IND-Enabling Studies; ** Also in development for psoriatic arthritis, ulcerative colitis and Crohn's disease; sc: subcutaneous

Pipeline of Proprietary and Partnered Programs

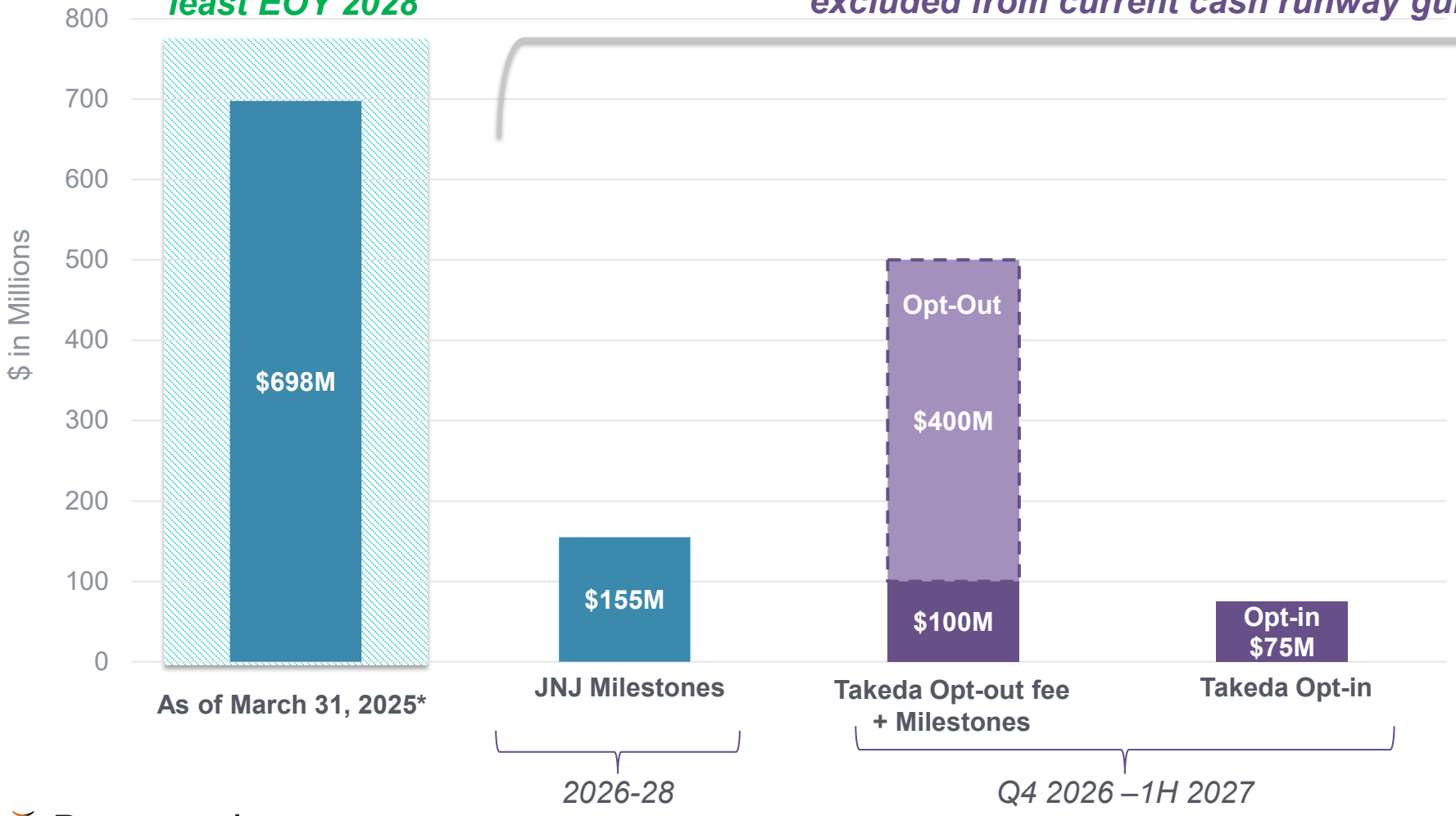


Protagonist On a Transformative Path Leading to Significant Potential Cash Inflows

2025-2028

Cash Runway expected through at least EOY 2028

Potential cash inflows excluded from current cash runway guidance



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

Q4 2026 and beyond

*represents total held in cash, cash equivalents and marketable securities as of March 31, 2025

Protagonist Therapeutics

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
- **$50M** (opt-in) **or $75M** (opt-out)
  NDA approval

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Financial Highlights

Financial Resources Forecast Extends Through At Least Q4 2028

CASH, CASH EQUIVALENTS & MARKETABLE SECURITIES

$697.8M

as of March 31, 2025

CASH RUNWAY FORECAST THROUGH AT LEAST

Q4 2028*

SHARES OUTSTANDING

~61.9M

as of March 31, 2025

*Based on cash, cash equivalents and marketable securities as of March 31, 2025, but excluding additional milestone payments, potential opt-out payments and future royalties

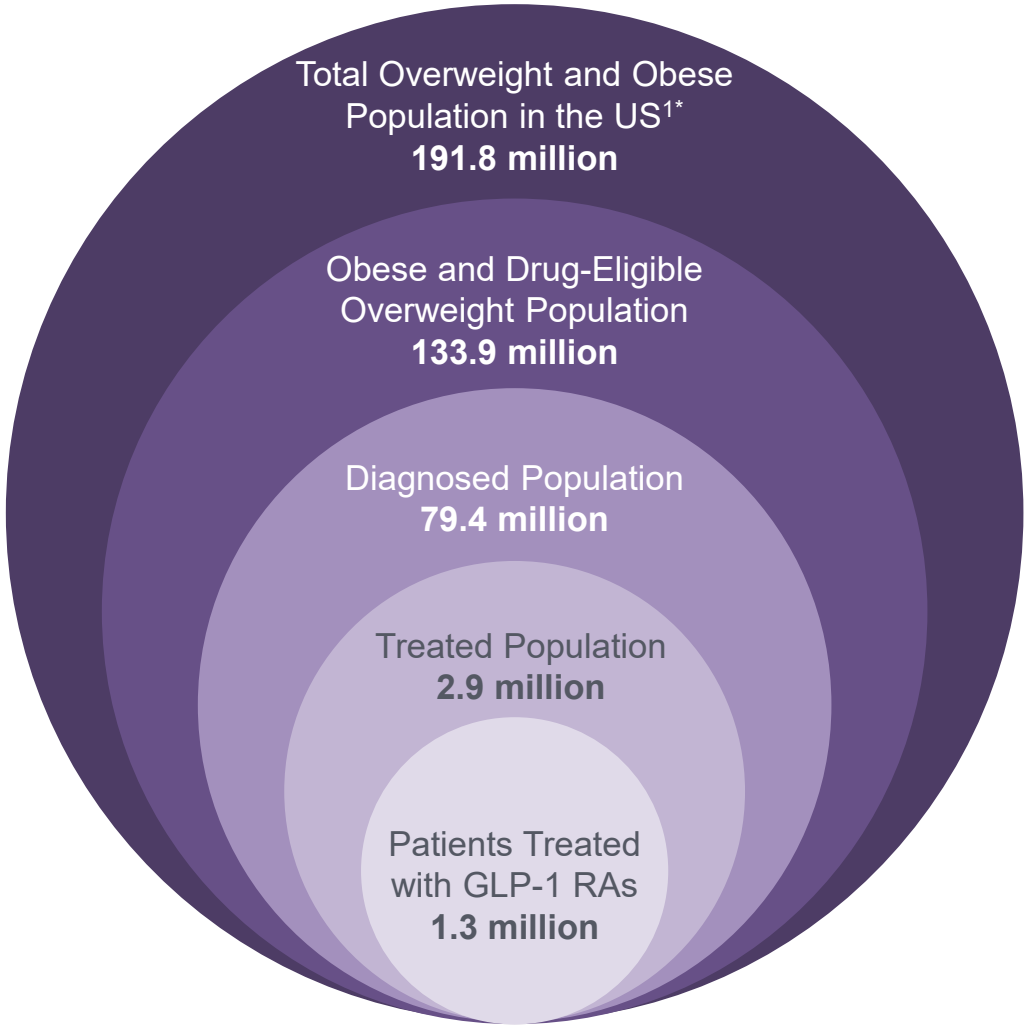
Protagonist Therapeutics

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

[1] Aronne LJ, NEJM 2025 (Ph3b open label head-to-head trial in non-diabetic obese patients)

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** ✓

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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

PN-477 is Orally Stable in Gastrointestinal Fluids

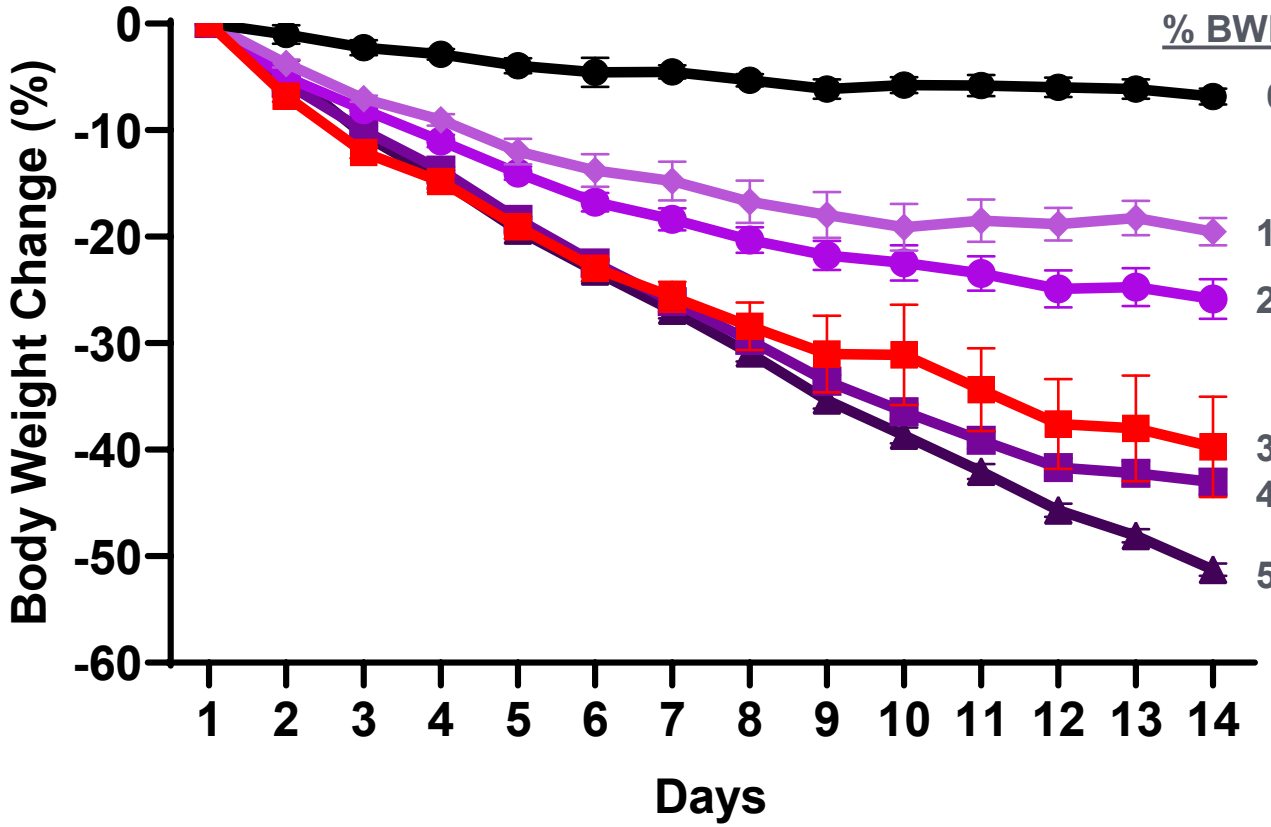
In Vitro Metabolic Stability

Compound	Simulated Gastric Fluid $T_{1/2}$ (hr)	Simulated Intestinal Fluid $T_{1/2}$ (hr)
PN-477	**> 24**	**15.9**
Retatrutide	**< 0.5**	**< 0.5**
Tirzepatide	**< 0.5**	**< 0.5**
Semaglutide	**< 0.5**	**< 0.5**

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)

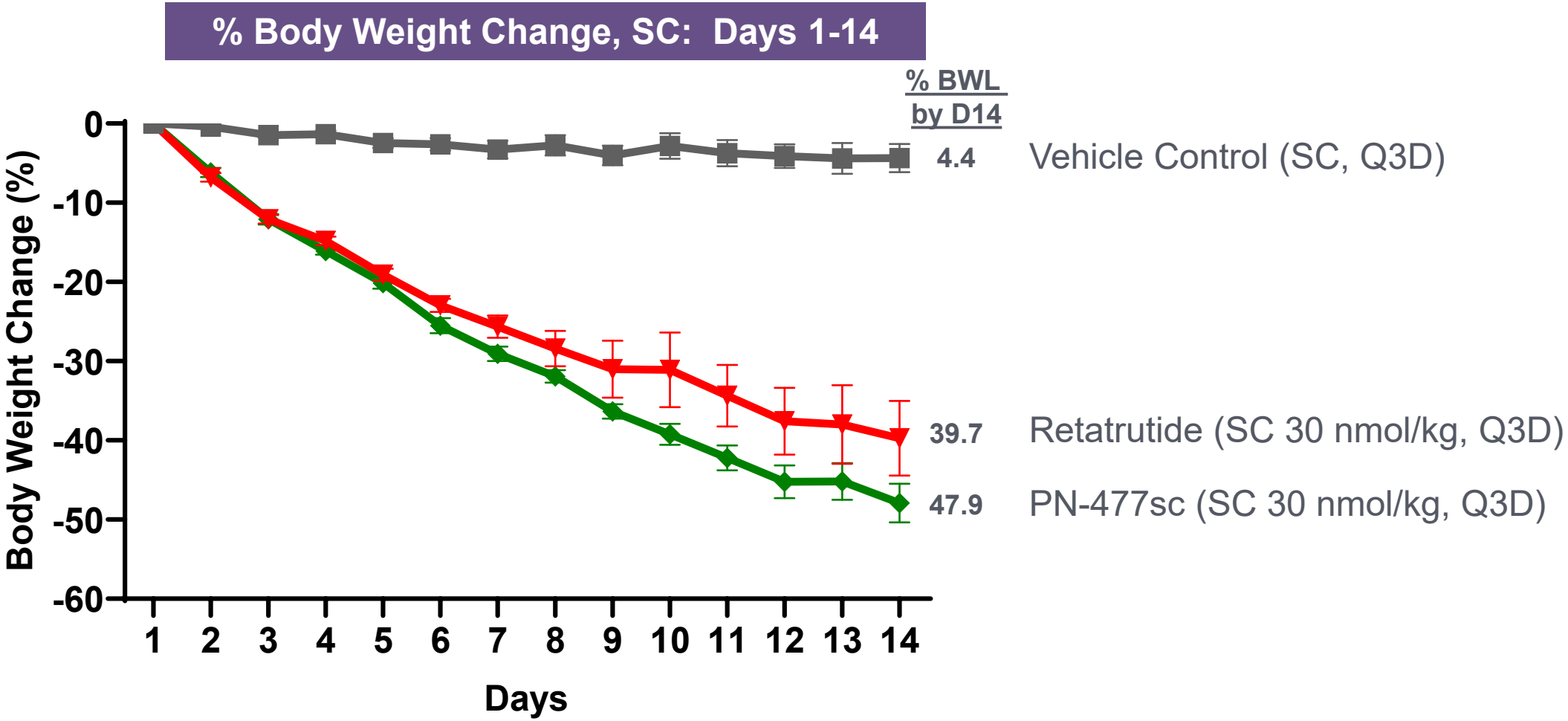
* Retatrutide SC 30 nmol/kg dose is the highest dose reported for DIO mouse efficacy study
(Cell Metabolism 34, 1234–1247, September 6, 2022)

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

Body Weight Loss and Body Composition Improvements Comparable to Retatrutide

DIO Mouse Study #2; Subcutaneous PN-477sc vs Retatrutide

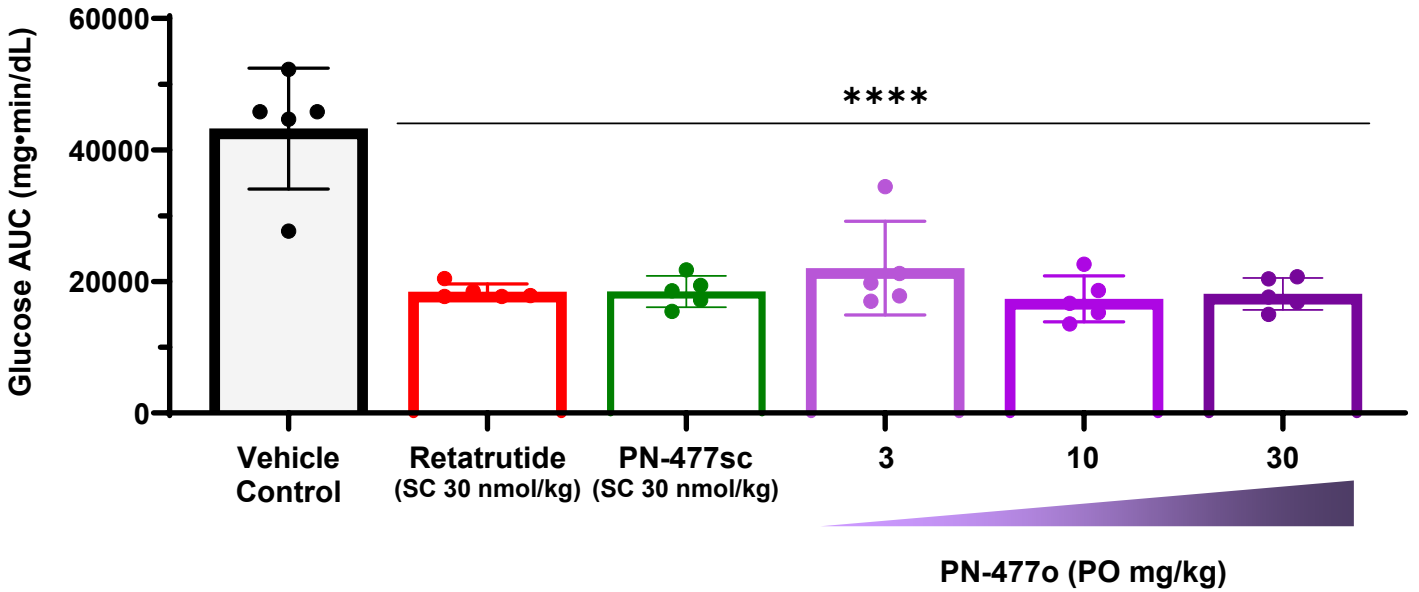
Body Composition	Retatrutide SC 30 nmol/kg Q3D	PN-477sc SC 30 nmol/kg Q3D
% Body Weight Loss (D22)	-31.5	-30.3
% Fat Mass Loss (D22)	-67.0	-70.0
% Lean Mass Loss (D22)	-16.8	-13.2
Lean Mass/Fat Mass Ratio		
- Baseline	1.3	1.4
- Day 22	3.3	3.9

DIO: Diet Induced Obese; SC: subcutaneous, 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

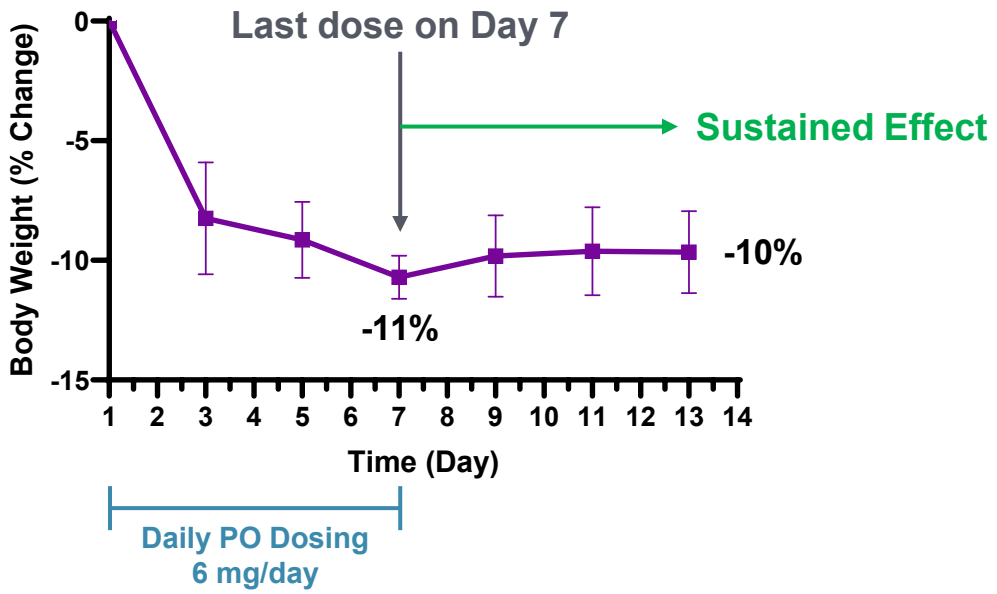
Protagonist Therapeutics

****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

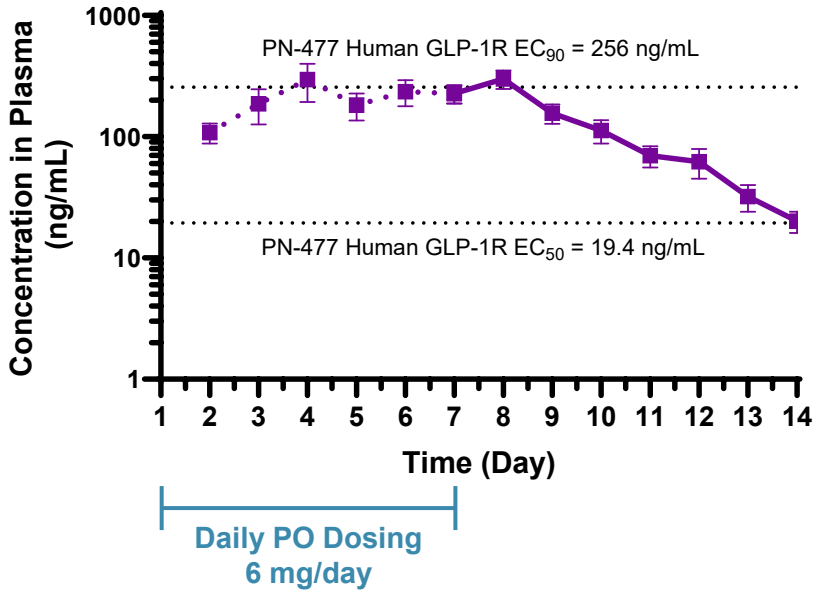
11% BW Loss by Day 7 in Cynomolgus Monkeys after 7-Day Oral Dosing of PN-477o

Weight Loss Sustained for 6 Days After Last Dose

Cyno % BW Change, PO



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



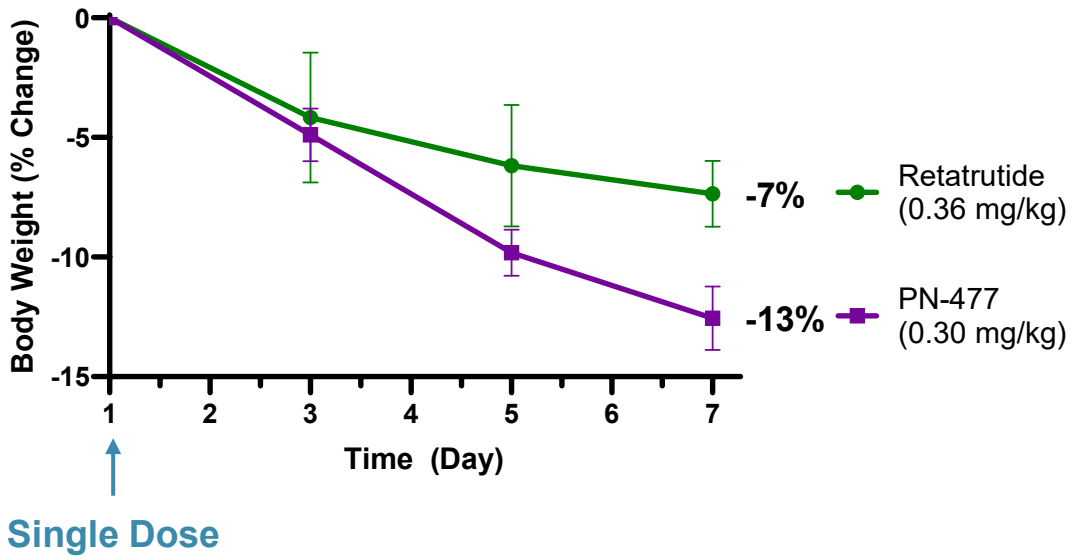
- PN-477o PK profile suggests once daily human dosing
- Body weight loss was sustained for 6 days post-last dose

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

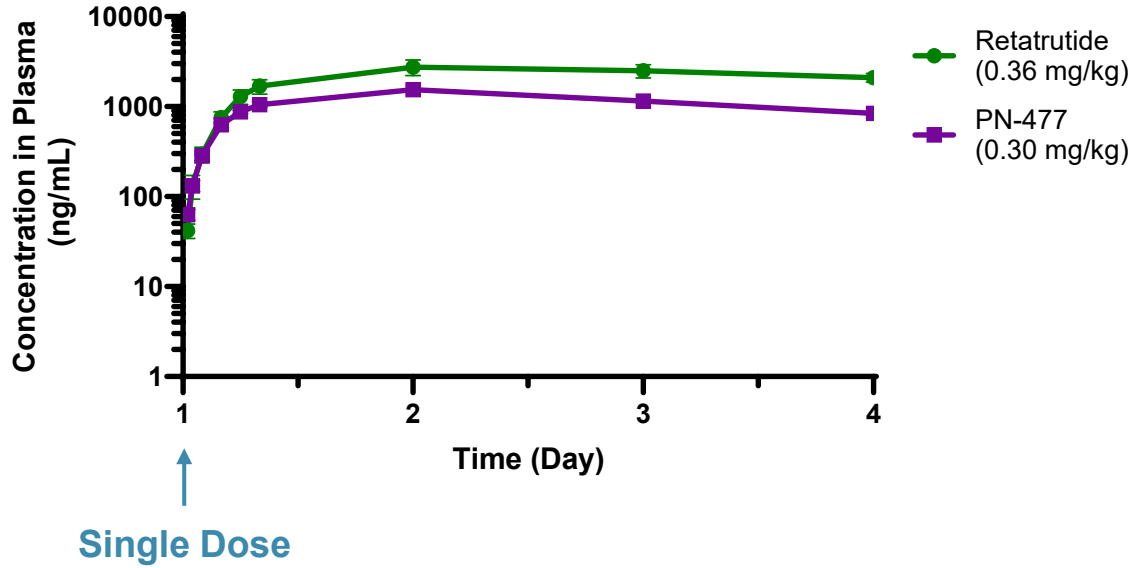
13% BW Loss by Day 7 in Normal Monkeys after Single SC Dose of PN-477

PN-477 Vs. Retatrutide

Cyno % BW Change, SC



Cyno PK, SC



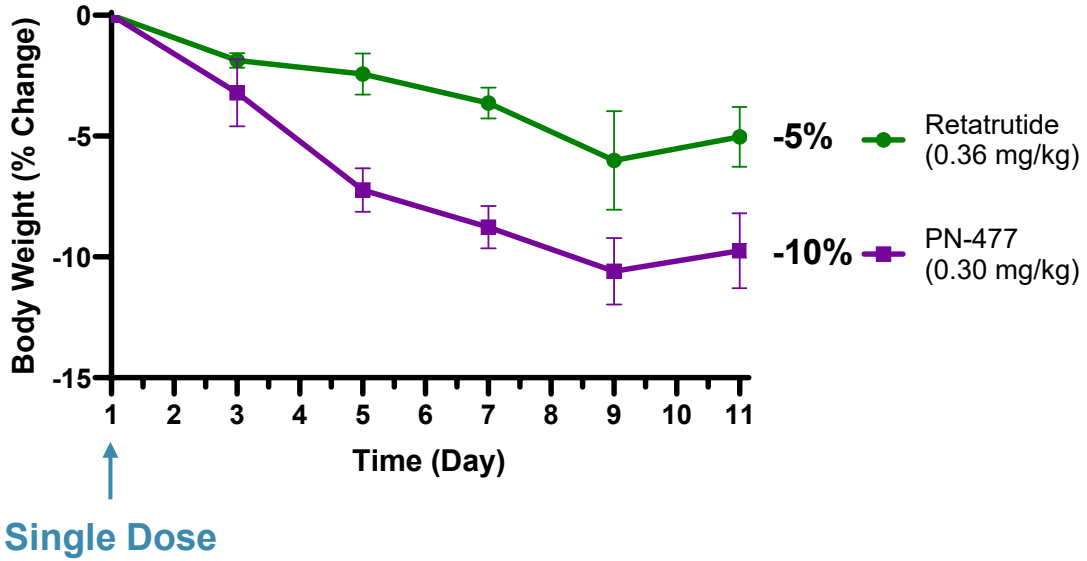
PN-477sc PK profile suggests once weekly human dosing

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

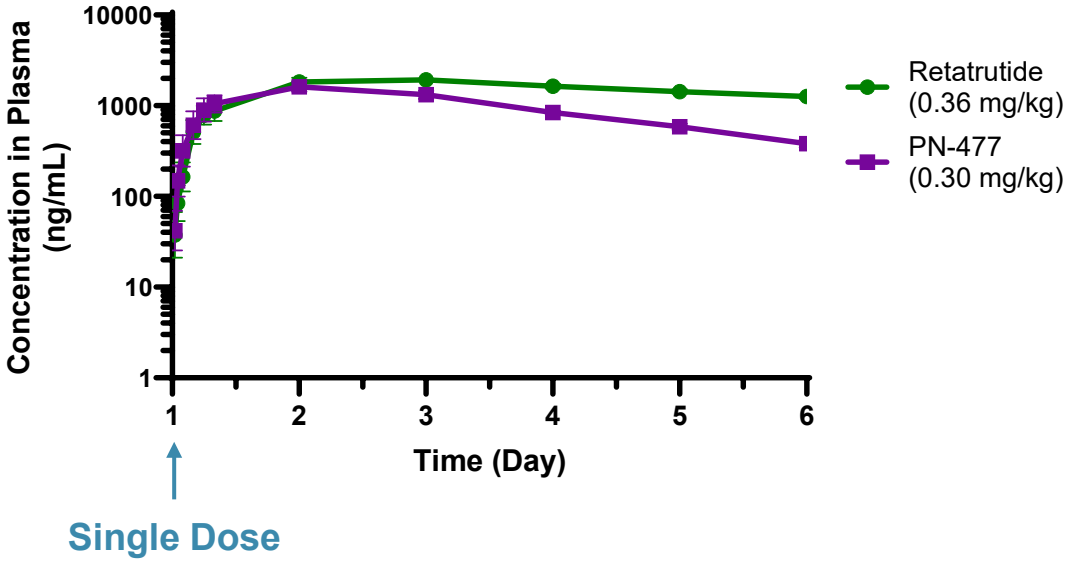
10% BW Loss by Day 11 in Normal Beagle Dogs after Single SC Dose of PN-477

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

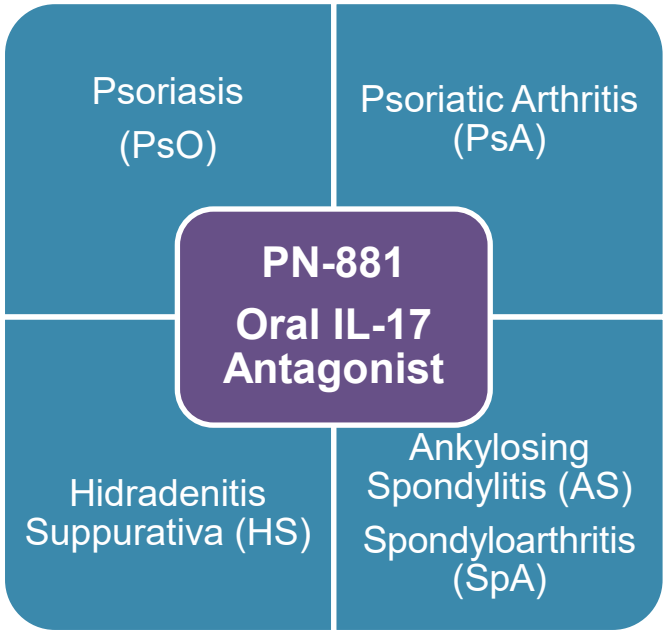
Protagonist Therapeutics

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



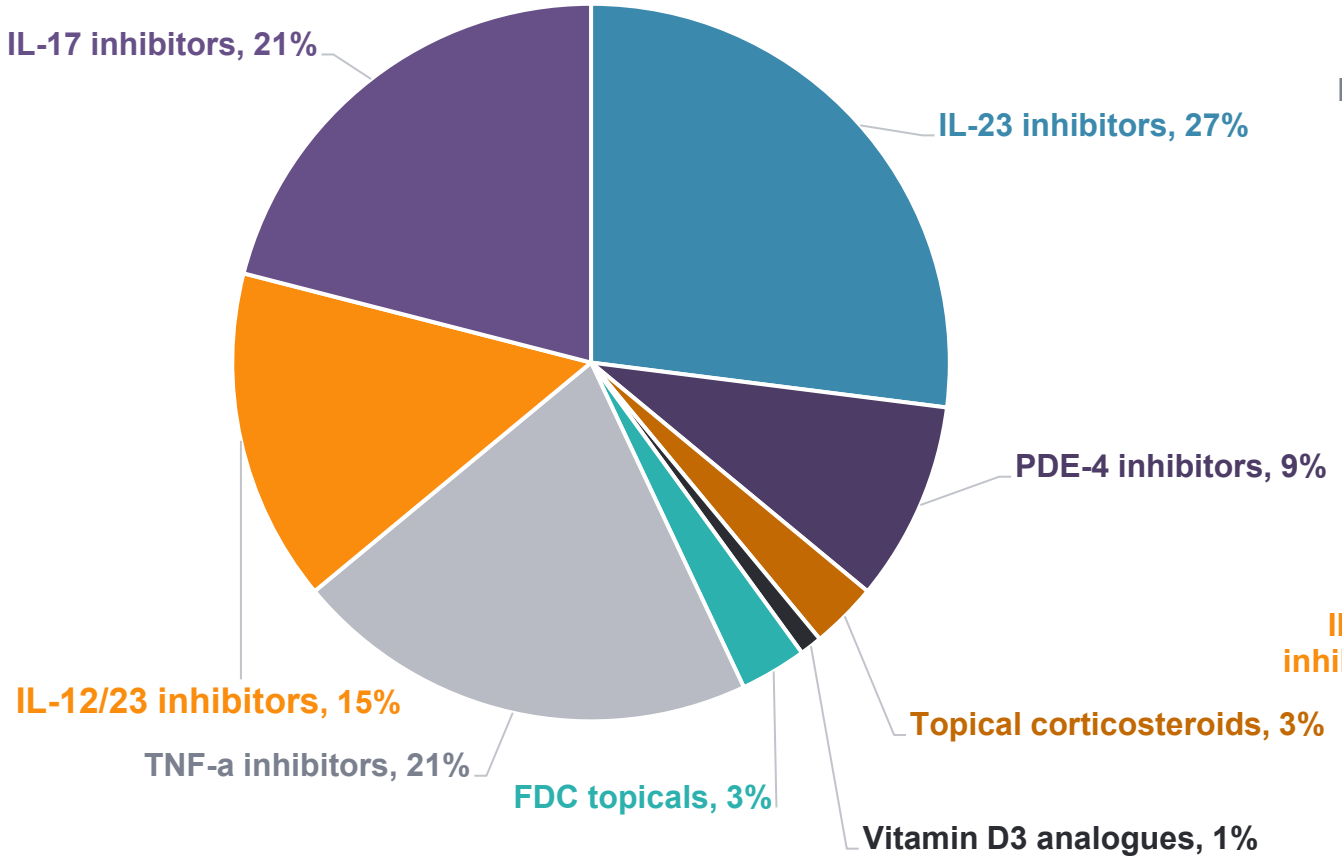
1. Psoriasis Disease Landscape and Forecast (Clarivate, 2023);
2. No approved oral IL-17 antagonists. Approved IL-17 mAbs: COSENTYX (secukinumab), TALTZ (ixekizumab), and BIMZELX (bimekizumab)
3. Blockade of both IL-17A and IL-17F leads to greater efficacy. Reich et al., N Engl J Med 2021;385:142-52.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

Protagonist Therapeutics

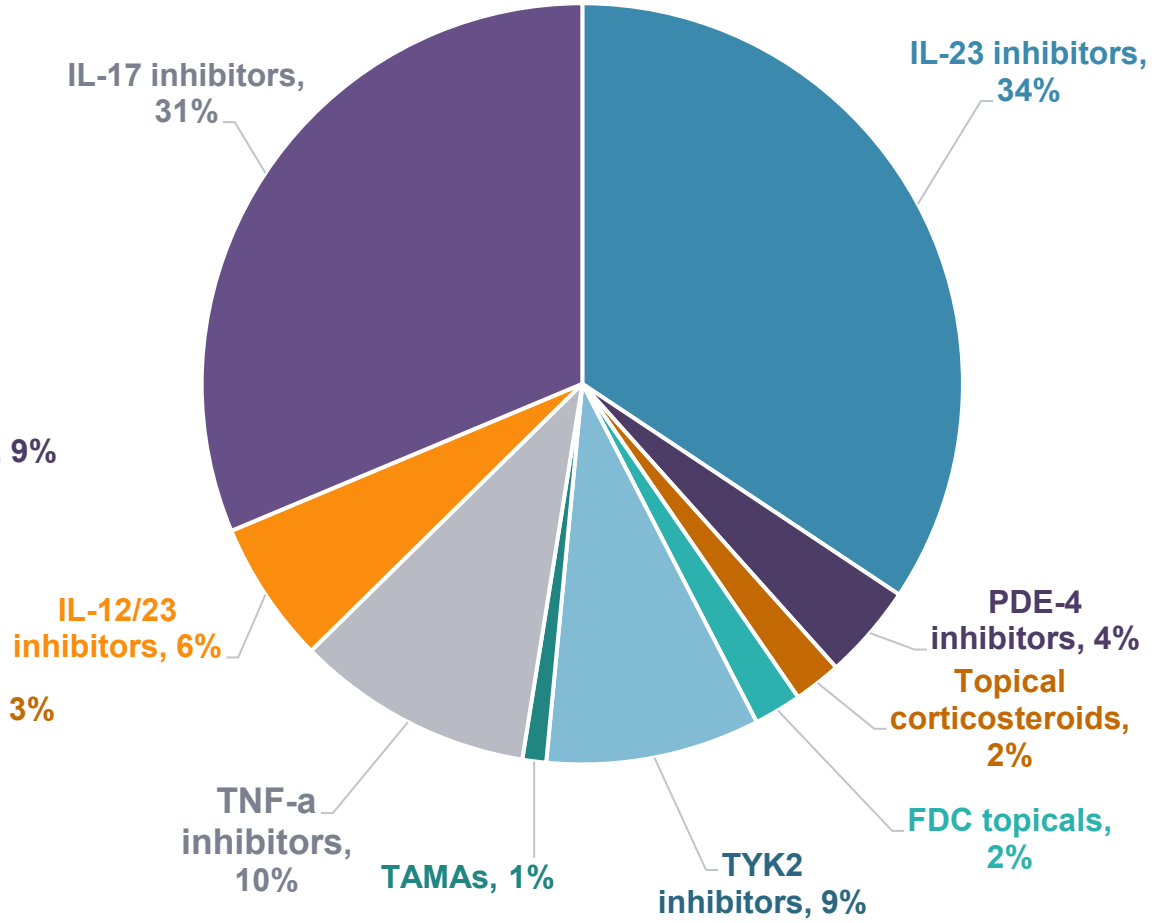
Psoriasis Market Share by Drug Class

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

2021 DISTRIBUTION
Market Size: $21.7B



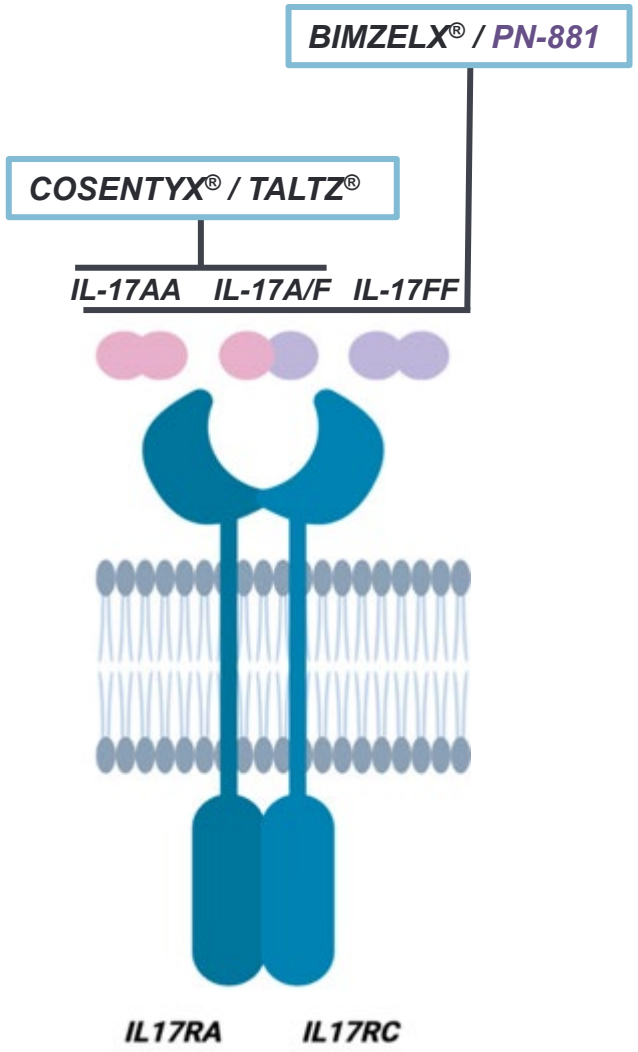
2031 DISTRIBUTION
Market Size: $30.1B



Protagonist Therapeutics

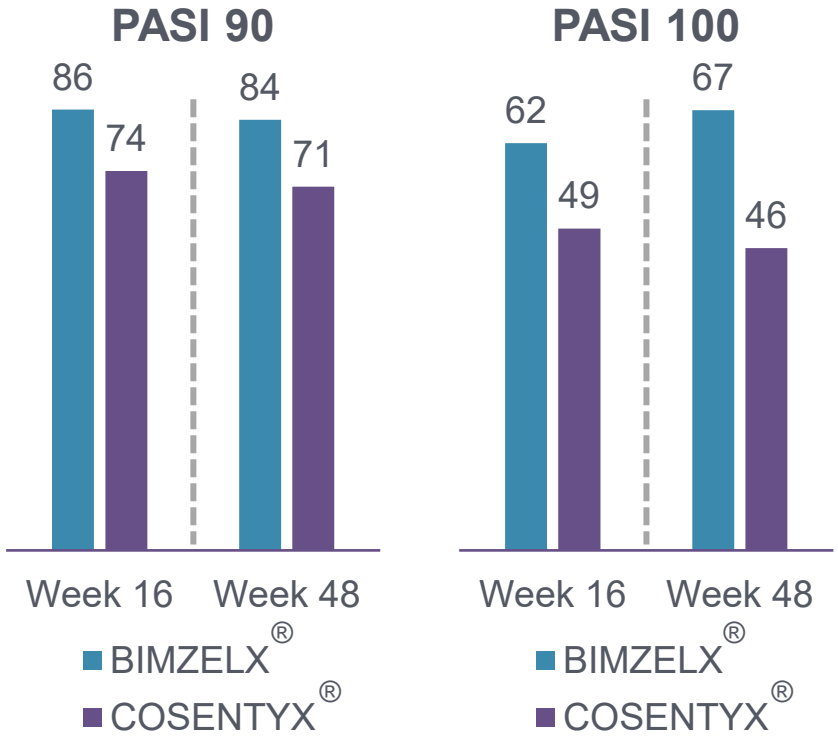
Psoriasis Disease Landscape and Forecast (Clarivate, 2023).

IL-17 Receptor Activated by Three Dimeric Forms of IL-17: IL-17AA, AF, and FF1



BE RADIANT Clinical Trial:

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



[1]Reich et al., N Engl J Med 2021;385:142-52. DOI: 10.1056/NEJMoa2102383

Selection of IL-17 Antagonist PN-881 as Development Candidate

Attribute	Criteria
Potency	• **Sub-nM potency vs IL-17 AA** ✓ • **Blocks three 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 ✓
In vivo Pharmacokinetics	• Mouse ✓ • Rat ✓ • Dog ✓ • Cynomolgus monkeys ✓
In vivo Pharmacodynamics	• Reduction in IL-17-induced CXCL1 after oral administration ✓
Tissue Distribution	• Mouse ✓ • Mini-pig ✓
Efficacy Model	• Rat IL-23-induced skin inflammation model ✓

Protagonist Therapeutics

PN-881 Potently Inhibits IL-17A and IL-17F

Similar potency as Bimzelx and ~100-fold more potent than Cosentyx

PN-881 vs Competitors	HT-1080 (nM)[1]					
	IL-17AA		IL-17AF		IL-17FF	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
Oral agents						
PN-881	**0.13**	**0.56**	**27**	**55**	**14**	**76**
DC-806[2] (or close analogue)	228	3323	ND	ND	Inactive	Inactive
Injectable agents						
Cosentyx®	11	118	151	604	Inactive	Inactive
Taltz®	0.12	0.35	ND[3]	ND[3]	Inactive	Inactive
Bimzelx®	0.17	0.32	19	26	13	16

1. Similar results observed in human dermal neonatal fibroblasts (HDFn) after stimulation with IL-17AA, IL-17AF, or IL-17FF
2. Compound #166 from DICE patent: US 2020/0247785 A1. DC-806 development discontinued & replaced with DC-111
3. ND = Not determined

Protagonist Therapeutics

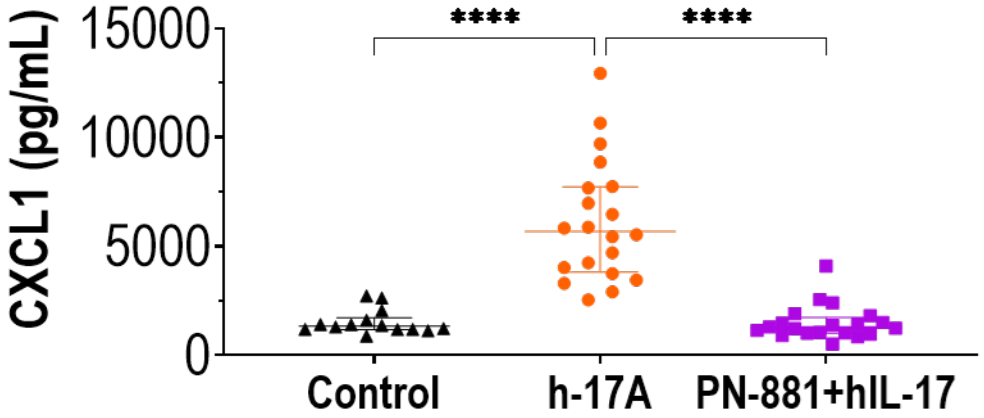
Oral PN-881 Neutralizes Human IL-17 in Mouse IL-17 Challenge PD Model

PN-881 Significantly Reduces Serum and Skin CXCL1 Levels After Oral Administration[1]

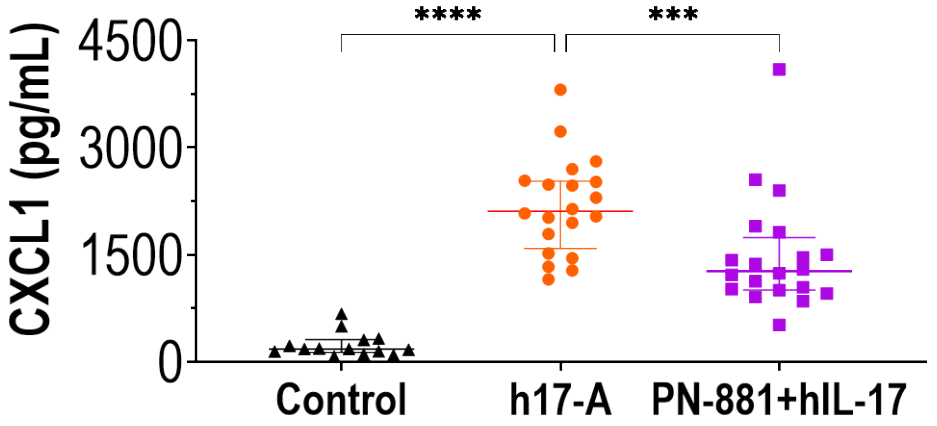
Treatment Groups:
a) Vehicle control
b) IL-17 alone
c) PN-881 (PO, QD)

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

Skin



Serum



- 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

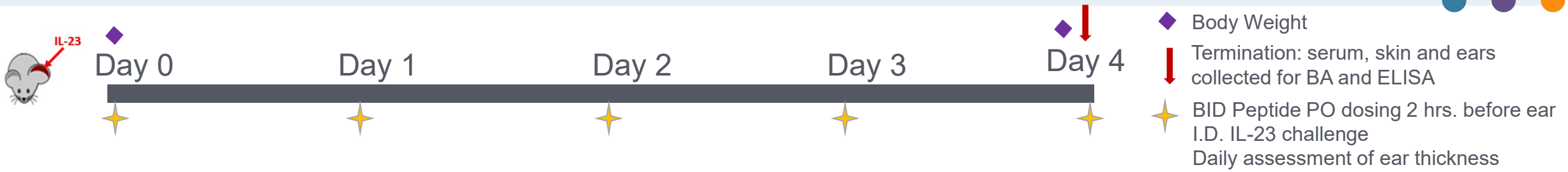
***p<0.001, ****p<0.0001 dot plot depict median and interquartile ranges,

1. Presented at Society for Investigative Dermatology (SID) conference, May 7-10, San Diego, CA, USA

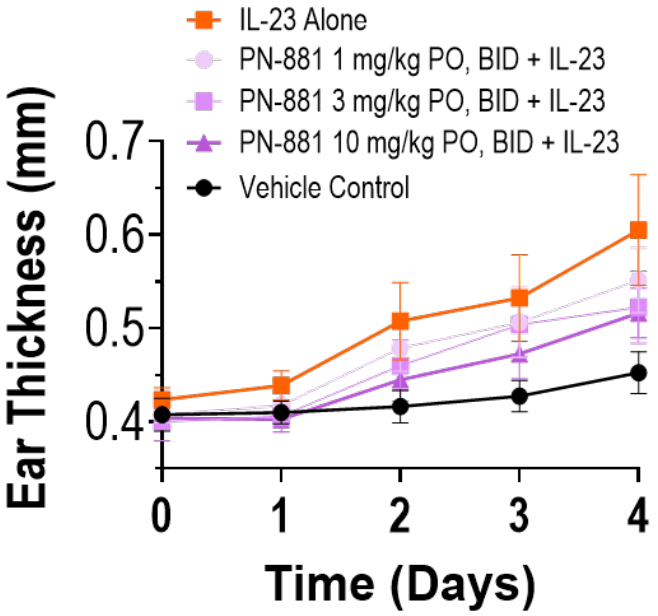
Protagonist Therapeutics

Oral PN-881 in the Rat IL-23-Induced Skin Inflammation Efficacy Model

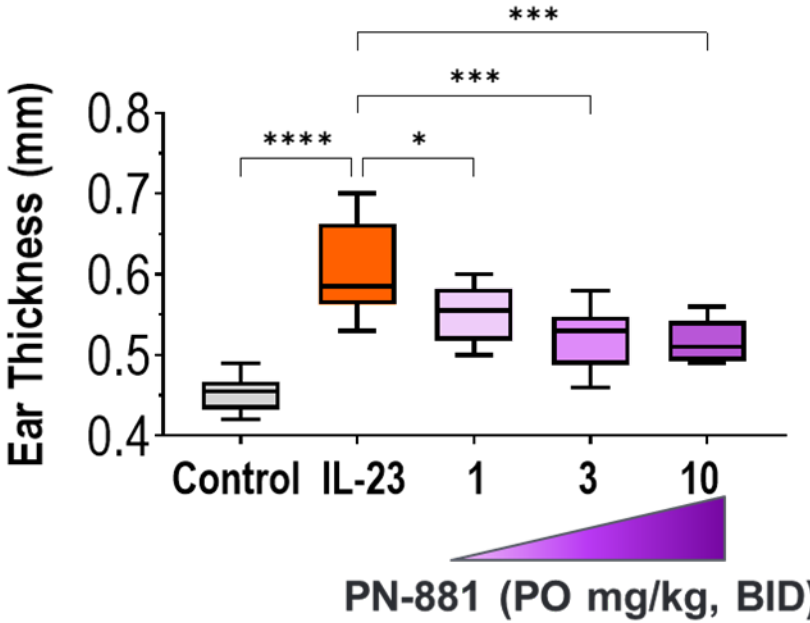
PN-881 Significantly Reduces IL-23-Induced Ear Thickness After Oral Administration[1]



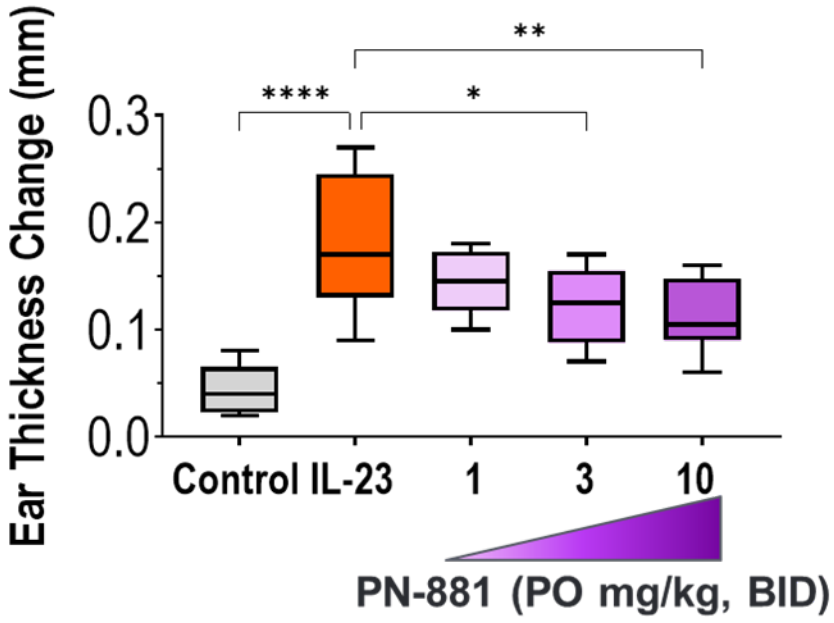
Ear Thickness Over Time



Ear Thickness (Day 4)



Ear Thickness Change



*p<0.05, **p<0.01, ***p <0.001, ****p <0.0001. Data points depict mean ± standard deviation, Boxes depict median and interquartile ranges; bars depict min. and max.

1. Presented at Society for Investigative Dermatology (SID) conference, May 7-10, San Diego, CA, USA

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: Near-Term Clinical Development Plan

Oral IL-17 Antagonist

H1 2025	H2 2025	H1 2026	H2 2026
❖ IND-Enabling Studies ❖ **SID'25 Meeting oral presentation**	❖ Initiation of 3-month Tox Studies ❖ Phase 1 Initiation	❖ **Phase 1 Topline PK/PD Results**	❖ Phase 2 Initiation

Protagonist Therapeutics

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**
- **Successful outcome in Phase 2b ulcerative colitis study**
  - **Broad Phase 3 campaign underway in both UC and Crohn's[3]**
- Potential annual peak sales of Icotrokinra: $5B+[1,2]
  - Tremfya® annual peak sales projected at $10B+[3]
  - Skyrizi® annual peak sales projected at $20B+ by 2027[4]
  - Psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease

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

Protagonist Therapeutics

Icotrokinra Psoriasis Clinical Studies Update

- **Phase 3 ICONIC-LEAD study[1]**
  - Co-primary endpoints (PASI 90 and IGA 0/1, week 16) met
    - Two-thirds (65%) of treated patients achieved IGA score of 0/1 (clear or almost clear skin) and 50% achieved a PASI 90 response, compared to 8% and 4% receiving placebo, respectively (P<0.001 for both endpoints) at Week 16
    - Continued skin clearance improvement was reported at Week 24 with 74% of patients treated with icotrokinra achieving IGA 0/1 and 65% achieving PASI 90
  - **Nearly half of patients treated with icotrokinra achieved completely clear skin – 46% reached IGA 0 and 40% reached PASI 100 at week 24**
  - Similar proportions of patients experienced adverse events (AEs) between icotrokinra (49%) and placebo groups (49%), with no new safety signals identified
- **Phase 3 ICONIC-ADVANCE 1&2 studies[2]**
  - Co-primary endpoints (IGA 0/1, PASI 90, Week 16) achieved; superiority to deucravacitinib in moderate-to-severe psoriasis established
  - All key secondary endpoints also met
- **Phase 3 ICONIC-ASCEND study initiation[2]**
  - The first-ever head-to-head study seeking to demonstrate the superiority of an oral pill, icotrokinra, compared to an injectable biologic, ustekinumab

Icotrokinra study results demonstrate its potential to shift treatment paradigm and set a new standard for treatment in plaque psoriasis

Protagonist Therapeutics

1. 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) 2025 Annual Meeting. March 2025; 2. Icotrokinra results show potential to set a new standard of treatment in plaque psoriasis. Johnson & Johnson. News release. 8 March 2025.

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; CD study planned

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

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 ✓
- **Phase 3 study** in ulcerative colitis · Planned

Crohn's Disease

- **Phase 3 study** in Crohn's disease · Planned

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

Psoriasis
NDA submitted
July 2025

Protagonist Therapeutics

ANTHEM-UC (NCT06049017): Icotrokinra (JNJ-2113) Phase 2b Study in Moderate to Severe Ulcerative Colitis (UC)

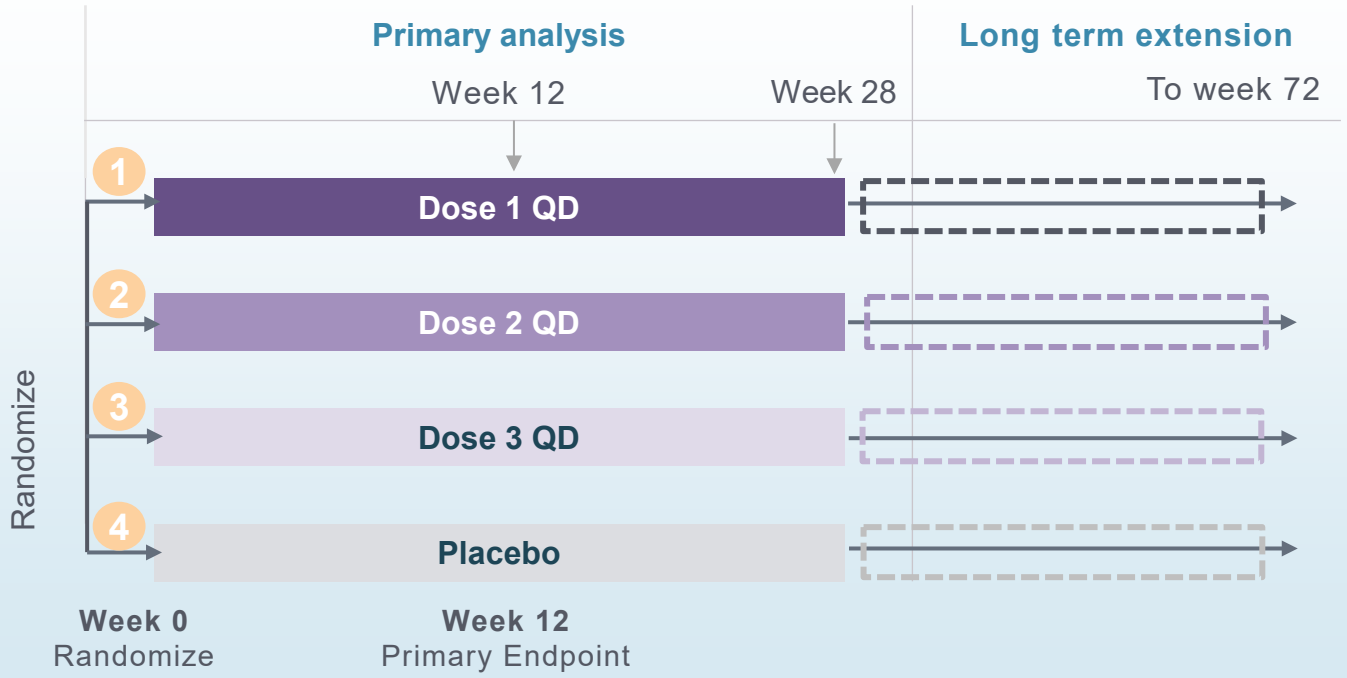
Adult Patients with UC
N = 252

Eligibility:

- 18 years of age or older
- Moderately to severely active UC as per the modified Mayo score
- Demonstrated inadequate response to or intolerance of conventional therapy and/or advanced therapy

Primary endpoint:

- Clinical Response (Modified Mayo score) at Week 12
- Primary Completion: 26 September 2024



Protagonist Therapeutics

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

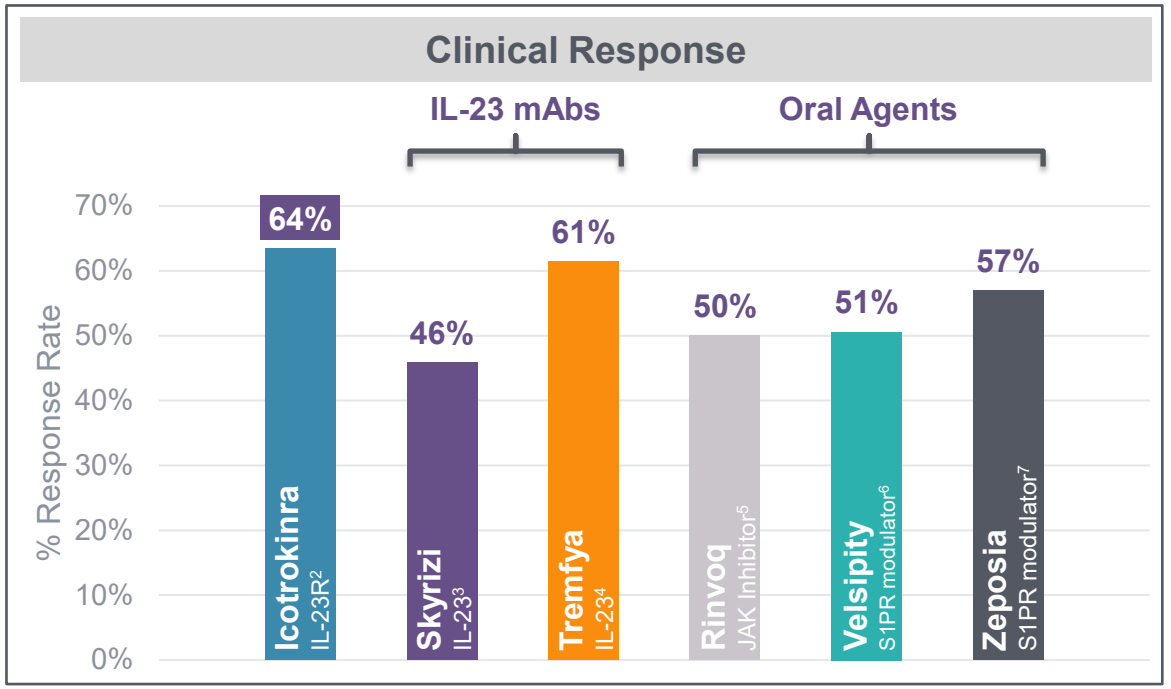
Icotrokinra has the potential to transform the treatment landscape in UC through its distinctive profile of efficacy, safety, tolerability, and convenience of a once-daily oral treatment.

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.

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

Clinical Response



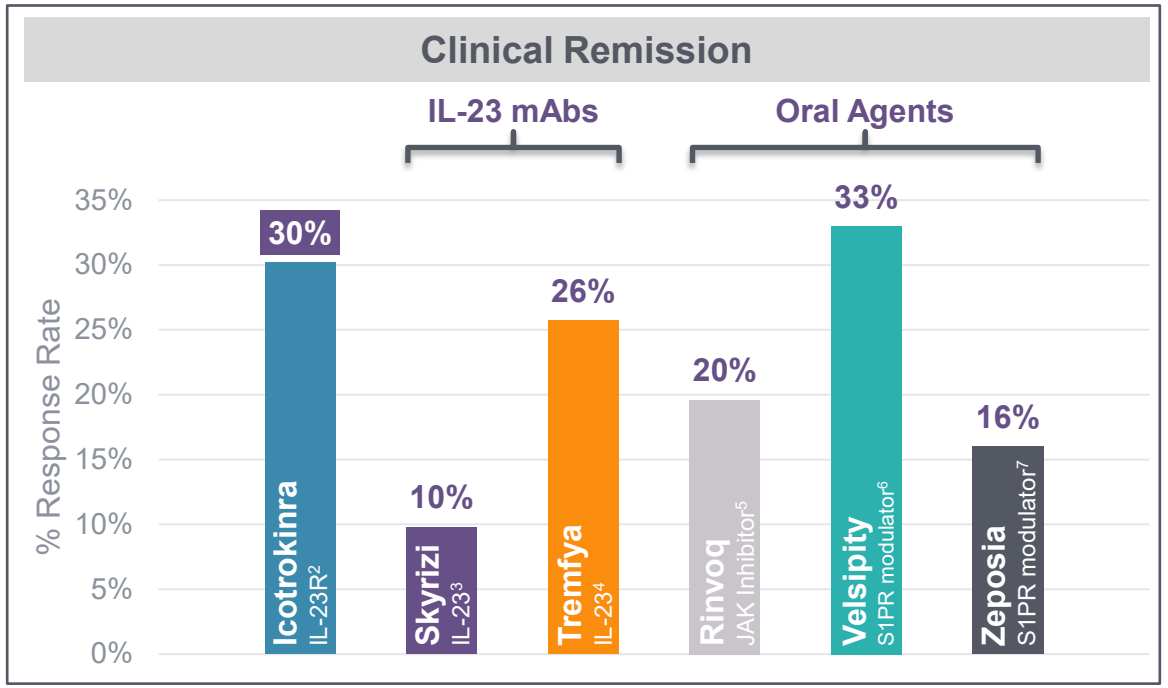
Agent	Endpoint Timeframe	Placebo Response (%)
Icotrokinra	Wk 12	27.0
Skyrizi	Wk 12	20.0
Tremfya	Wk 12	27.6
Rinvoq	Wk 8	13
Velsipity	Wk 12	32.5
Zeposia	Wk 8	37

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

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 planned

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
- Phase 3 UC study is planned

Crohn's Disease (CD)

- Phase 3 CD study is planned

Protagonist Therapeutics

Takeda

Rusfertide
A Synthetic Mimetic of the Natural Hormone Hepcidin

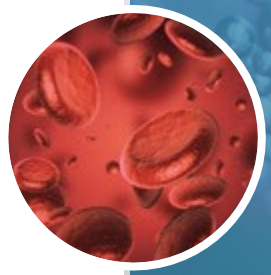
Addressing Unmet Needs in Polycythemia Vera

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 with Moderate Treatment Burden

Defining the “moderate treatment burden" population 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.

Marketed Agents for PV are Cytoreductive Therapies

No Approved Medications That Specifically Target Red Blood Cells and Hematocrit

Interferon

Pegasys®, Besremi®

Interferons have long been used off-label in PV treatment; Besremi is the first interferon product approved for PV[1]

Slow onset of action, with average time to response of **1.2 to 1.4 years**[2]

Failed to show noninferiority to HU at 12 months in the PROUD-PV study[3]

Black box warning for serious neuropsychiatric, autoimmune, ischemic, and infectious disorders[2]

Ruxolitinib

Jakafi®

Only approved for hydroxyurea-resistant or intolerant patients[4]

Improves splenomegaly, a potential marker of disease progression[5]

Potential serious side effects include thrombocytopenia, neutropenia, and anemia[4]

23% of patients were found to have discontinued ruxolitinib within a mean of **2 years** post treatment initiation[6]

1. Gilreath JA, et. al. *Blood*. 2018;132 (Supplement 1). 2. Besremi FDA label. 3. Gisslinger H, et. al. *Lancet Haematol*. 2020;7(3):e196-e208. 4. Jakafi FDA label. 5. Coltoff R, et. al. *Clin Lymphoma Myeloma Leuk*. 2020;20(10):697-703. 6. Tremblay, D, et al. *Leuk Res*. 2021;109:106629.

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 and **Fast Track** status 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

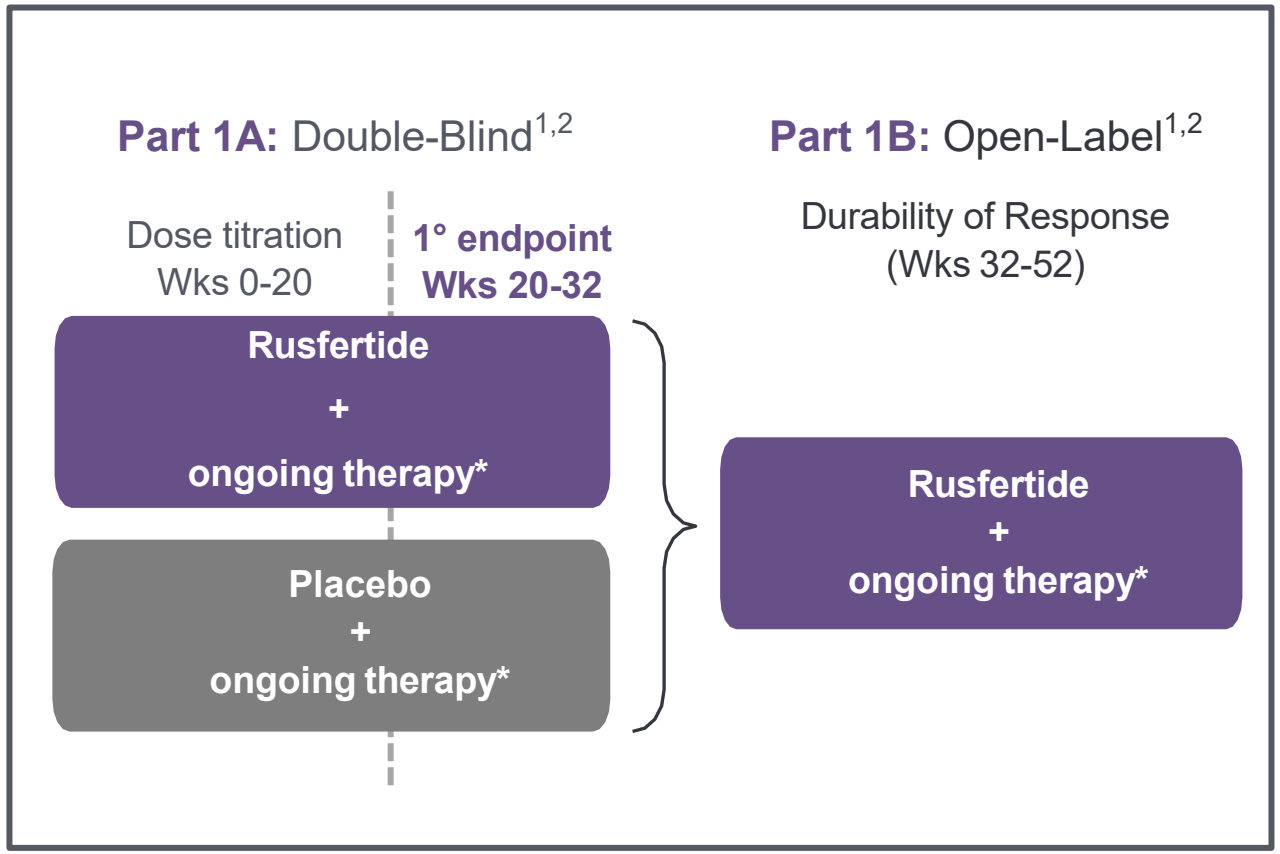
ASCO 2025 Plenary Session

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]

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

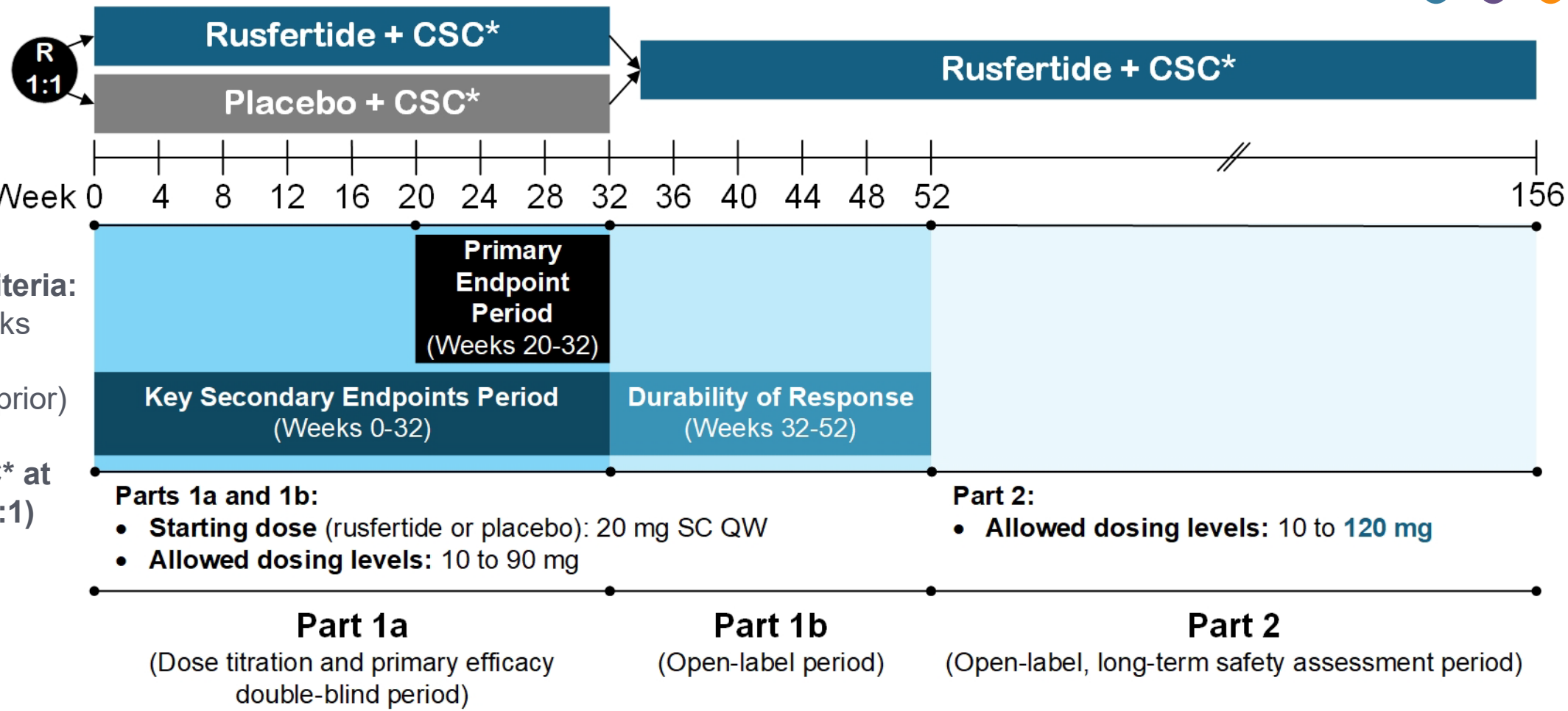
Protagonist Therapeutics

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

Phase 3 VERIFY Study (NCT05210790) Design in PV[1]

Key Inclusion Criteria:
≥3 PHL (28 weeks prior) OR
≥5 PHL (1 year prior)

Stratified by CSC* at randomization (1:1)



*PHL ± CRT
CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera; QW, once-weekly; R, randomization; SC, subcutaneous.

Protagonist Therapeutics

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

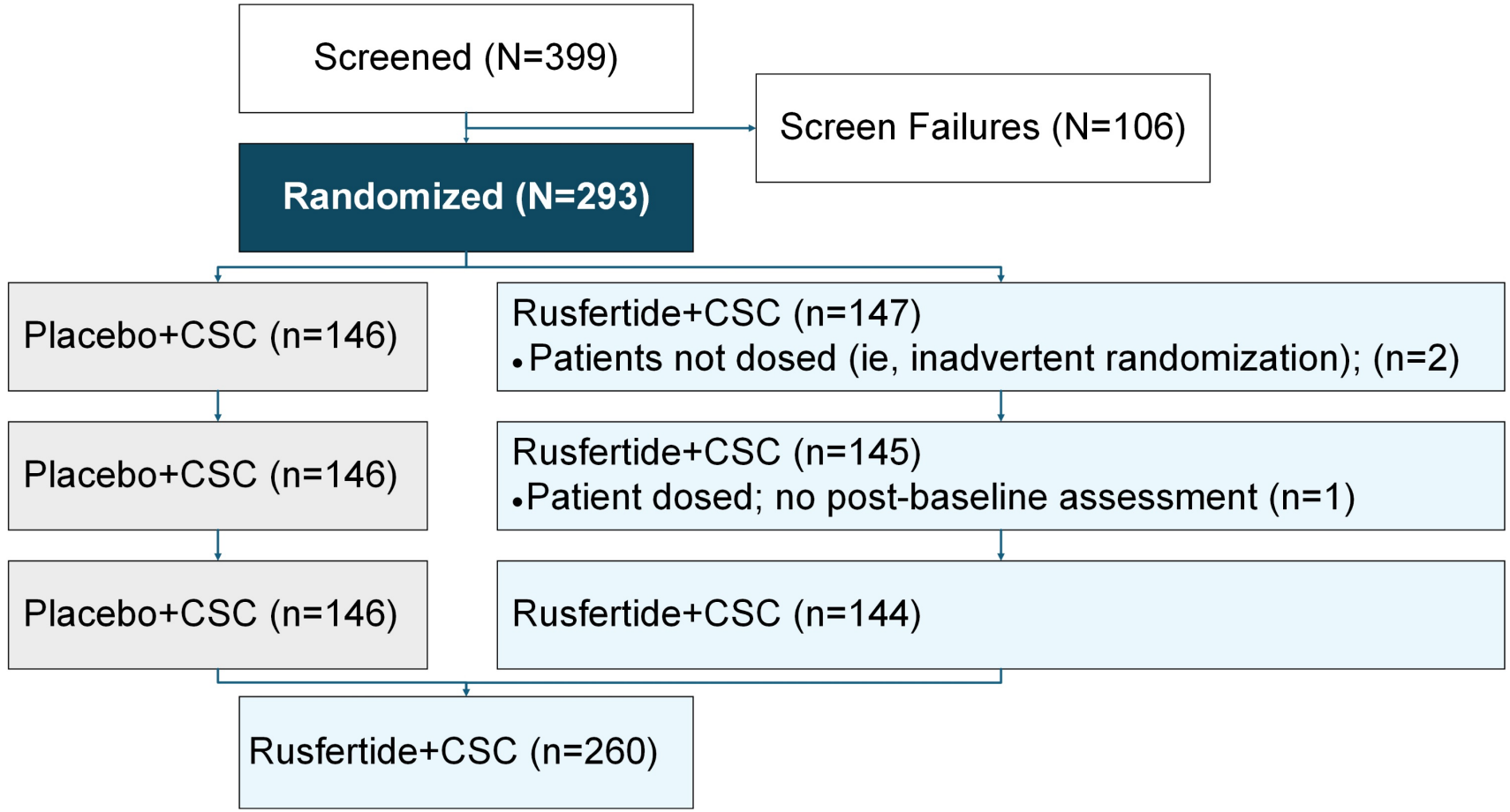
Phase 3 VERIFY Study (NCT05210790) in PV
Prespecified Primary and Key Secondary Endpoints[1]

- **Rusfertide with CSC vs placebo with CSC:**
  - **Primary endpoint (US FDA): Weeks 20-32**
    - Clinical response (absence of phlebotomy eligibility, ie, confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%)
  - **Key secondary endpoints: Weeks 0-32**
    - Mean number of phlebotomies (**EU EMA**)
    - Proportion of patients with Hct <45%
    - Mean change from baseline in PROMIS Fatigue SF-8a Score
    - Mean change from baseline in MFSAF TSS7

CSC, current standard-of-care; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; Hct, hematocrit; MFSAF TSS, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score; PROMIS, Patient-Reported Outcomes Measurement Information System PV, polycythemia vera; SF, short form.

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

VERIFY Patient Disposition and Analysis Sets: Part 1a[1]



FAS, all randomized patients according to the treatment assigned at randomization (ITT principle) who received at least one dose of study drug and had a baseline and at least one postbaseline assessment in Part 1a. CSC, current standard-of-care.

Data cutoff: 7 January 2025

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

Baseline Demographics and Disease Characteristics[1]

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)	Total (N=293)
Age, years, median (range)	57 (27-82)	58 (28-86)	57 (27-86)
Gender, n (%)			
Male	108 (74.0)	106 (72.1)	214 (73.0)
Female	38 (26.0)	41 (27.9)	79 (27.0)
Risk Category, n (%)			
High risk (age ≥60 years old and/or prior TE)	70 (47.9)	66 (44.9)	136 (46.4)
Disease Characteristics			
Age at PV diagnosis (years), median (range)	51 (22-81)	53 (17-84)	52 (17-84)
PV duration (years), median (range)	3 (0.2-29.2)	2.8 (0.2-26.4)	2.9 (0.2-29.2)
Phlebotomy History – 28 Weeks Prior to Study Treatment			
Number of TPs, mean ± SD	4.1 ± 1.4	4.2 ± 1.6	4.2 ± 1.5
Patients requiring ≥7 TPs, n (%)	7 (4.8)	16 (10.9)	23 (7.8)

Data cutoff: 7 January 2025

CSC, current standard-of-care; PV, polycythemia vera; SD, standard deviation; TE, thromboembolic event; TP, therapeutic phlebotomy.

Protagonist Therapeutics

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

Concurrent Cytoreductive Therapy During Part 1a[1]

n (%)	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)	Total (N=293)
Patients With Concurrent Cytoreductive Medication	81 (55.5)	83 (56.5)	164 (56.0)
Hydroxyurea	57 (39.0)	58 (39.5)	115 (39.2)
Interferons			
Interferon, peginterferon alpha-2a, or ropeginterferon alfa-2b	20 (13.7)	19 (12.9)	39 (13.3)
JAK1/JAK2 Inhibitor			
Ruxolitinib	3 (2.1)	5 (3.4)	8 (2.7)

CSC, current standard-of-care; JAK, Janus Kinase.

Data cutoff: 7 January 2025

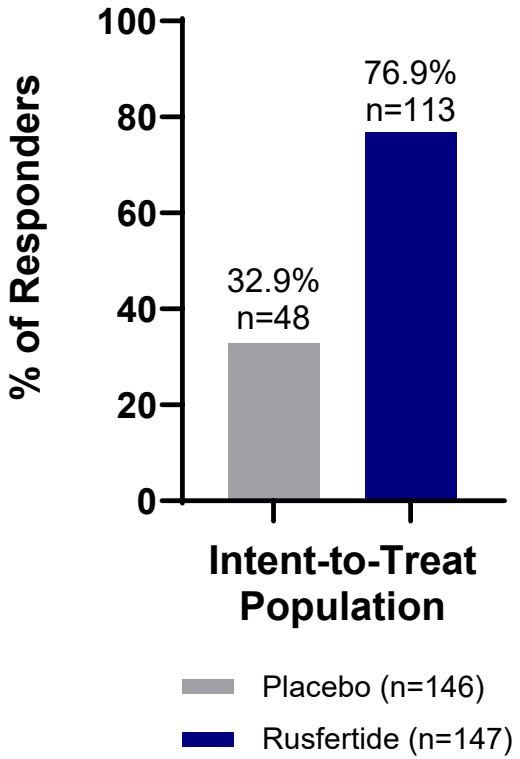
Protagonist Therapeutics

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

VERIFY Study Met Its Primary Endpoint During Weeks 20-32 (Part 1a)[1]

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Responders, n (%)[a]	48 (32.9)	113 (76.9)
p-value*		**<0.0001**
Non-responders, n (%)	98 (67.1)	34 (23.1)

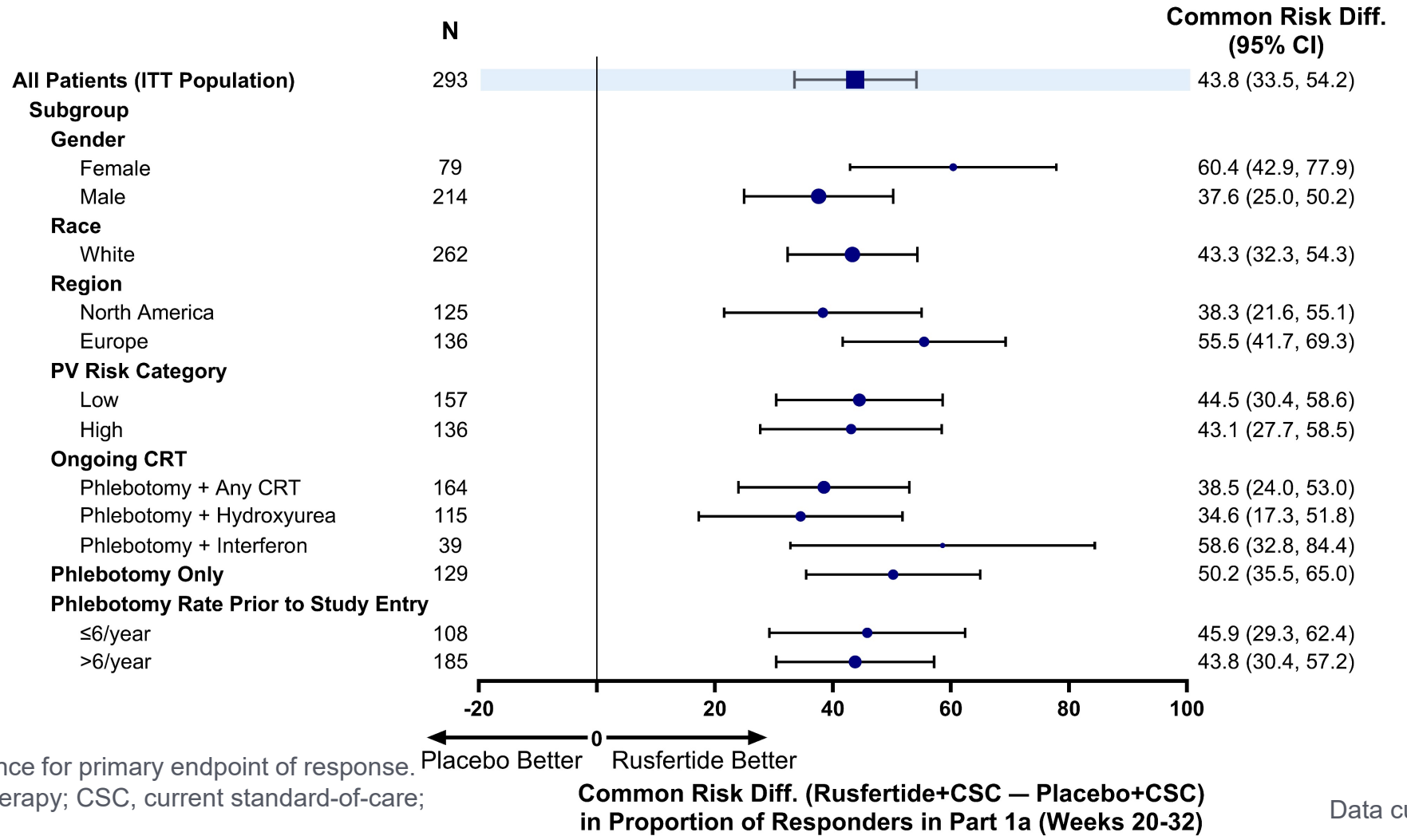
[a]Responder = absence of phlebotomy eligibility (confirmed Hct ≥45% and ≥3% higher than baseline Hct OR Hct ≥48%), no phlebotomies, and completion of Part 1a.
*p-value based on Cochran-Mantel-Haenszel test.
Hct, hematocrit.



Data cutoff: 7 January 2025

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

Rusfertide + CSC Benefit Maintained vs. Placebo + CSC for Response* Across Subgroups, Including Risk Status and Concurrent Therapy[1]



*Common risk difference for primary endpoint of response.
CRT, cytoreductive therapy; CSC, current standard-of-care; ITT, intent to treat.

Data cutoff: 7 January 2025

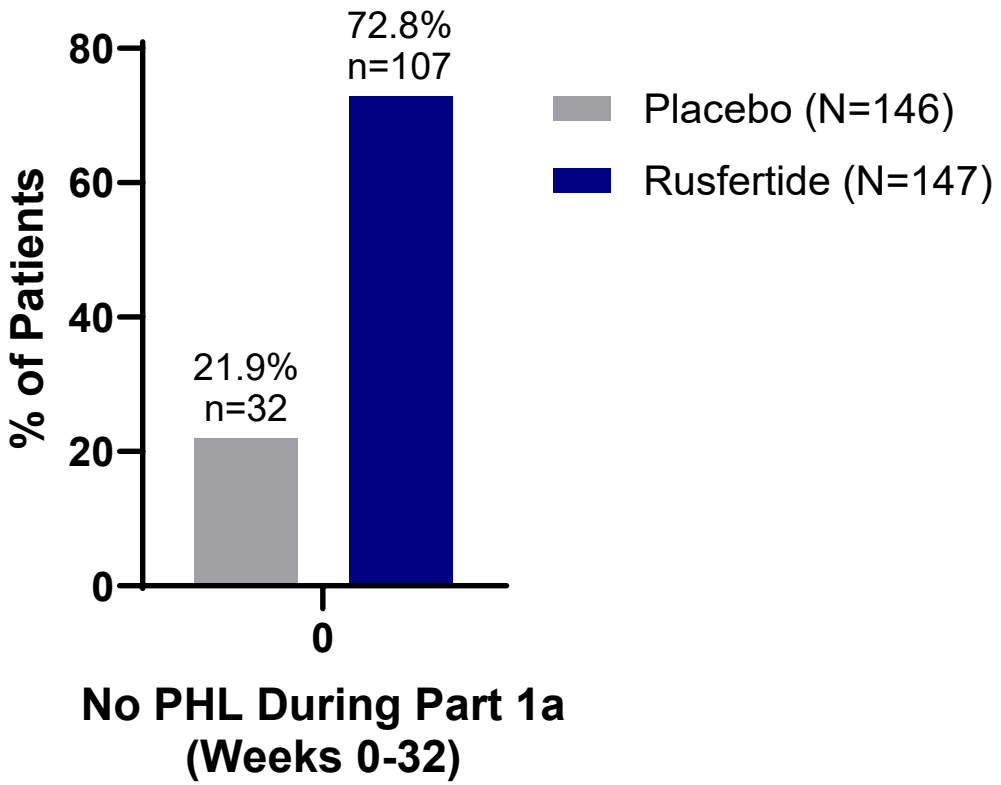
Protagonist Therapeutics

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

Rusfertide + CSC Reduced the Mean Number of PHL From Weeks 0-32 vs Placebo + CSC (p<0.0001): Key Secondary Endpoint #1[1]

Number of Phlebotomies	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Mean (SD)	1.8 (1.5)	0.5 (1.2)
p-value*	<0.0001	

*p-value associated with the LS means difference.
LS, least-squares; SD, standard deviation.



- Rusfertide reduced the mean number of PHL (Weeks 0-32) vs. placebo by a statistically significant margin across subgroups, including PV risk category, geographic region, and use of concurrent CRT

CRT, cytoreductive therapy; CSC, current standard-of-care; PHL, phlebotomy; PV, polycythemia vera.

Data cutoff: 7 January 2025

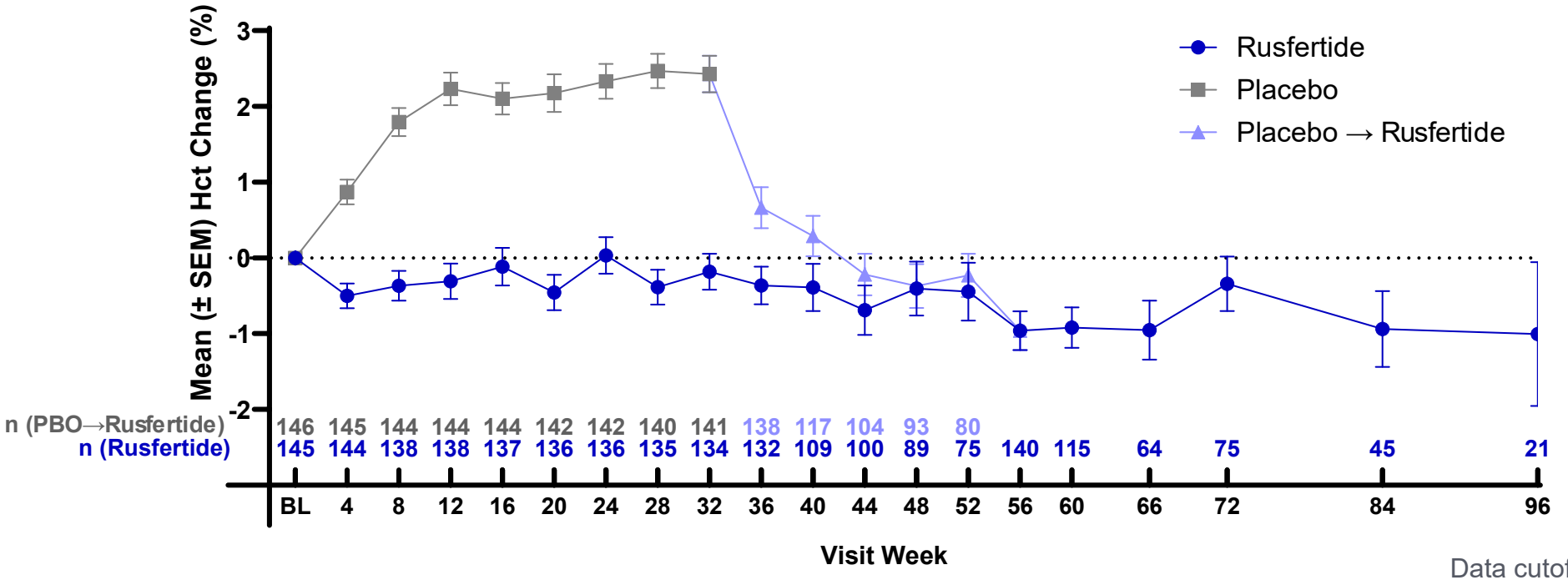
Protagonist Therapeutics

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

Rusfertide + CSC More Likely to Maintain Hct <45% From Weeks 0-32 vs Placebo + CSC: Key Secondary Endpoint #2[1]

	Placebo + CSC (n=146)	Rusfertide + CSC (n=147)
Hct <45% (Baseline through Week 32), n (%)[a]	21 (14.4)	92 (62.6)
p-value*		**<0.0001**

[a]Hct <45% from baseline through Week 32 (a single Hct ≥45% was allowed, excluding intercurrent events classified as non-responders).
*Cochran-Mantel-Haenszel test.



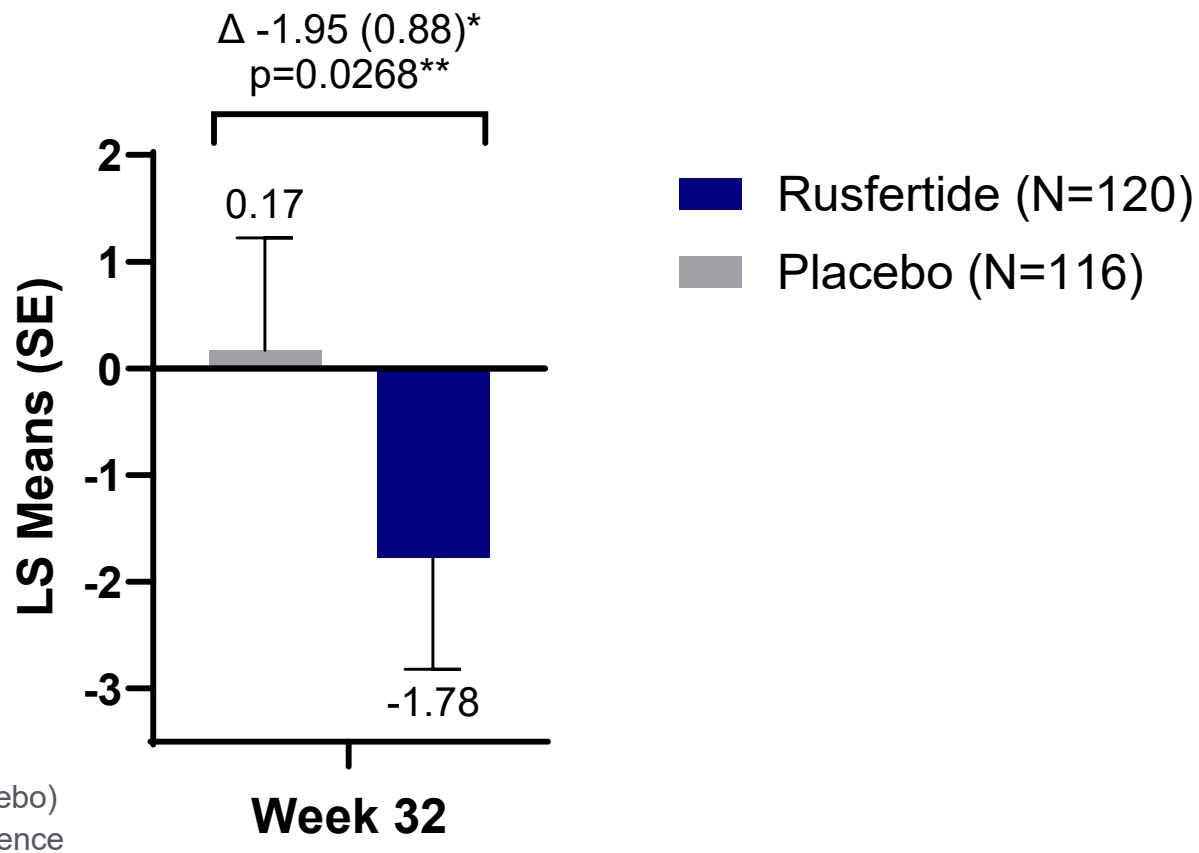
Data cutoff: 7 January 2025

CSC, current standard-of-care; Hct, hematocrit; PBO, placebo; SEM, standard error of measurement.

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

Rusfertide Demonstrated an Improvement in the PROMIS Fatigue SF-8a Total T-Score at Week 32 vs. Placebo: *Key Secondary Endpoint #3*[1]

LS Means Difference at Week 32:



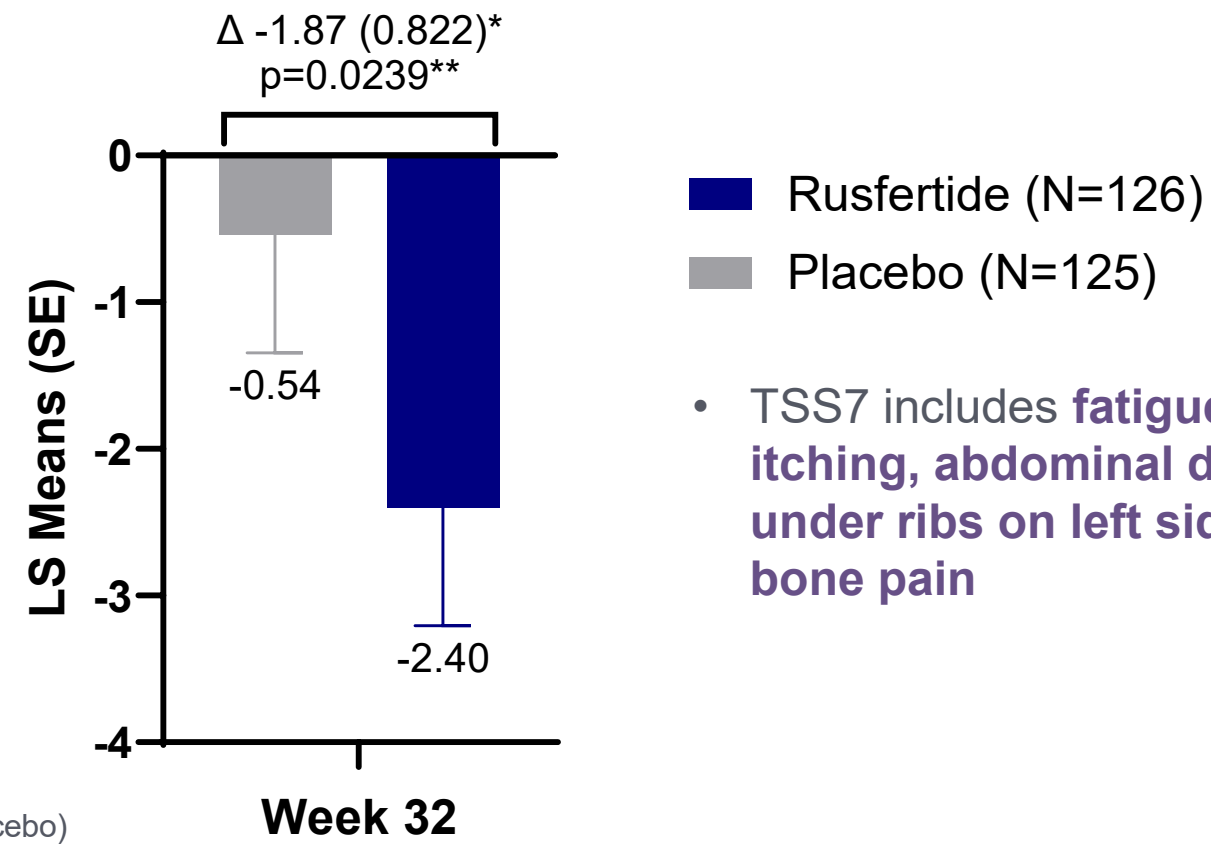
*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error; SF, short form.

Data cutoff: 7 January 2025

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

Rusfertide Demonstrated an Improvement in the MFSAF TSS7 at Week 32 vs. Placebo: Key Secondary Endpoint #4[1]

LS Means Difference at Week 32:



- TSS7 includes **fatigue**, **night sweats, itching, abdominal discomfort, pain under ribs on left side, early satiety,** and **bone pain**

*LS means (SE) difference (rusfertide – placebo)
**p-value associated with the LS mean difference
LS, least-squares; MFSAF TSS7, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score-7 item; SE, standard error. Data cutoff: 7 January 2025

Protagonist Therapeutics

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

VERIFY: Key PRO-Related Secondary Endpoints at Week 32

Includes All Patients* Regardless of Symptom Status at Baseline

Instrument	Symptom(s)		Endpoint Description Comparison of rusfertide to placebo:
PROMIS Fatigue SF-8a[1,2]	SF-8a	Fatigue	• Mean change from baseline at end of Part 1a (Week 32) in the PROMIS SF-8a total T-score
MFSAF version 4.0[3,4]	TSS-7	Fatigue	• Mean change from baseline at end of Part 1a (Week 32) in the MFSAF v4.0 TSS7
		Night sweats	
		Itching	
		Abdominal discomfort	
		Pain under the ribs	
		Early satiety	
		Bone pain	

*Patients were not required to have symptoms (e.g., fatigue, night sweats, itching, etc.) to enroll in VERIFY.

MFSAF TSS7, Myelofibrosis Symptom Assessment Form version 4.0 Total Symptom Score 7; PRO, patient reported outcomes; PROMIS Fatigue SF-8a, Patient Reported Outcomes Measurement Information System (PROMIS®) Fatigue Short Form 8a; PV, polycythemia vera; TSS, total symptom score.

1. Garcia SF, et al. *J Clin Oncol*. 2007;25:5106-12; 2. Cella D, et al. *J Clin Epidemiol*. 2016;73:128-34; 3. Mesa RA, et al. *Leuk Res*. 2009;33:1199-203; 4. Gwaltney C, et al. *Leuk Res*. 2017;59:26-31.

Protagonist Therapeutics

Exposure and Treatment-Emergent Adverse Events (Part 1a)*[1]

- Median treatment exposure was 32 weeks in both groups
  - Median (min, max) dose was 30 (10, 90) mg in the rusfertide group
- The most common TEAEs in the rusfertide group included localized injection site reactions and anemia
- Discontinuation rates due to TEAEs were 2.7% (placebo) and 5.5% (rusfertide)

Most Frequent TEAEs (≥6.5% in either group) in Part 1a, n (%)	Placebo + CSC (n=146)	Rusfertide + CSC (n=145)
Patients with at least 1 TEAE	126 (86.3)	129 (89)
Injection site reactions[a]	48 (32.9)	81 (55.9)
Anemia	6 (4.1)	23 (15.9)
Fatigue	23 (15.8)	22 (15.2)
Headache	17 (11.6)	15 (10.3)
COVID-19	16 (11.0)	14 (9.7)
Pruritus	14 (9.6)	14 (9.7)
Diarrhea	8 (5.5)	12 (8.3)
Dizziness	9 (6.2)	12 (8.3)
Arthralgia	12 (8.2)	11 (7.6)
Constipation	11 (7.5)	11 (7.6)
Abdominal distension	8 (5.5)	10 (6.9)
Thrombocytosis	0	10 (6.9)

*Safety analysis set.
AE, adverse event; CSC, current standard-of-care; TEAE, treatment-emergent adverse event.

[a]Injection site reactions (grouped term); all other TEAEs are preferred terms.

Protagonist Therapeutics

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

Cancer Events and Serious TEAEs (Part 1a)*[1]

- 10 skin malignancies (including 1 melanoma) detected prior to randomization
- During Part 1a, non-PV cancer events were reported in 8 patients

Cancer Events	Placebo + CSC (n=146)	Rusfertide + CSC (n=145)
Patients with ≥1 Cancer Event, n (%)	7 (4.8)	1 (0.7)
Basal cell carcinoma	3 (2.1)	0
Squamous cell carcinoma	1 (0.7)	1 (0.7)
Malignant melanoma	1 (0.7)	0
Colorectal cancer	1 (0.7)	0
Prostate cancer	1 (0.7)	0

- Serious AEs occurred in 3.4% (rusfertide) and 4.8% (placebo) of patients (none related to rusfertide)
- There was 1 TE (acute MI; occurred ~2 weeks after treatment initiation) reported in the rusfertide group

*Safety analysis set.
AE, adverse event; MI, myocardial infarction; TE, thromboembolic event; TEAE, treatment-emergent adverse event.

Data cutoff: 7 January 2025

Protagonist Therapeutics

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

Conclusions[1]

- Rusfertide is an investigational weekly subcutaneous injection for PV
- In the phase 3 VERIFY study that included patients with PV who were receiving CSC, rusfertide met its primary endpoint and all four key secondary endpoints vs. placebo
  - In VERIFY Part 1a, rusfertide:
    - Significantly reduced the PHL eligibility and improved Hct vs. placebo
    - Demonstrated a statistically significant improvement in symptoms (assessed using two PRO instruments)
- Rusfertide demonstrated a manageable safety profile consistent with prior studies
- **Rusfertide represents a potential new treatment option for PV**
  - These data will be used to file marketing authorizations throughout the world

CRT, cytoreductive therapy; CSC, current standard-of-care; Hct, hematocrit; PHL, phlebotomy; PRO, patient-reported outcome; PV, polycythemia vera.

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 will be presented at key medical meetings in 2025 and included in regulatory filings (eg, NDA, MAA)

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

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.

Protagonist Therapeutics

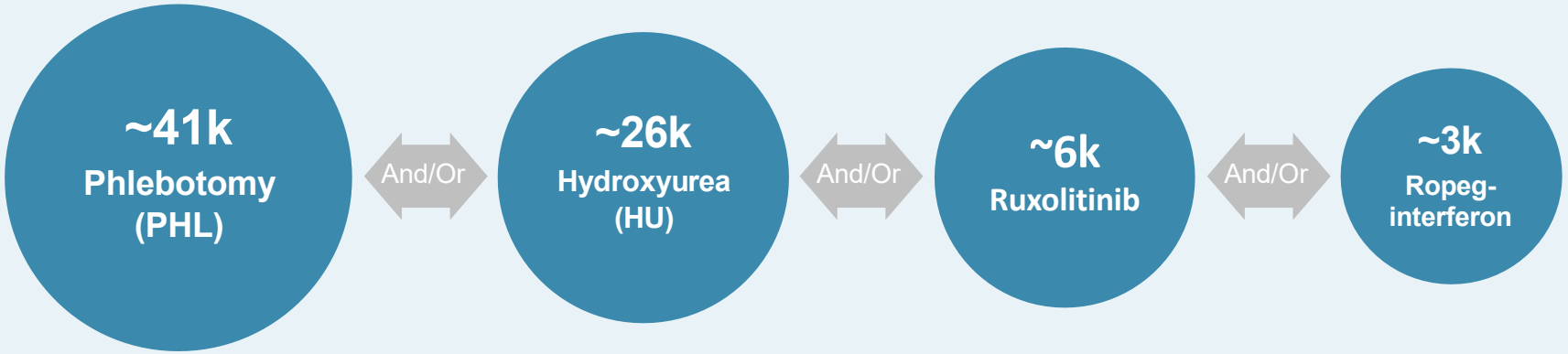
Polycythemia Vera: Prevalence, Treatment Paradigm and Unmet Need

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

Major Upcoming Catalysts in 2H 2025 and 2026

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

	1H 2025	2H 2025	1H 2026	2H 2026
Rusfertide (Takeda)	❖ PV day[1] ✓ ❖ **VERIFY topline results[2]** ✓ ❖ **ASCO VERIFY plenary presentation[3]** ✓	❖ **NDA filing[4]** ❖ ASH Meeting[4]	❖ Medical Conferences	❖ **US Approval (PV)**
Icotrokinra (Johnson&Johnson Innovative Medicine)	❖ Medical Conferences ✓ ❖ **Ph2b UC ANTHEM[2]** ✓ ❖ Study initiation: • Ph3 ICONIC-PsA 1[2] ✓ • Ph3 ICONIC-PsA 2[2] ✓ • Ph3 ICONIC-ASCEND (H2H vs. Stelara) ✓ ❖ Ph3 PsO ADVANCE 1 ✓ ❖ Ph3 PsO ADVANCE 2 ✓	❖ **Psoriasis NDA submitted July '25** ✓ ❖ Medical Conferences	❖ Medical Conferences	❖ **US Approval (Psoriasis)** ❖ Ph3 ICONIC-PsA 1 Primary Completion
Discovery	**1. PN-477o** ✓ **2. PN-477sc** ✓ Anti-obesity DCs[5]	❖ **PN-881 Ph1 initiation[4]** ❖ Oral Hepcidin DC[4]	❖ **PN-477 Ph1 initiation[6]**	❖ **PN-881 Ph2 Initiation[7]**

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

Protagonist Therapeutics

Protagonist Therapeutics

Thank you