



COMPANY OVERVIEW

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President & CEO

December 02, 2024

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, 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.

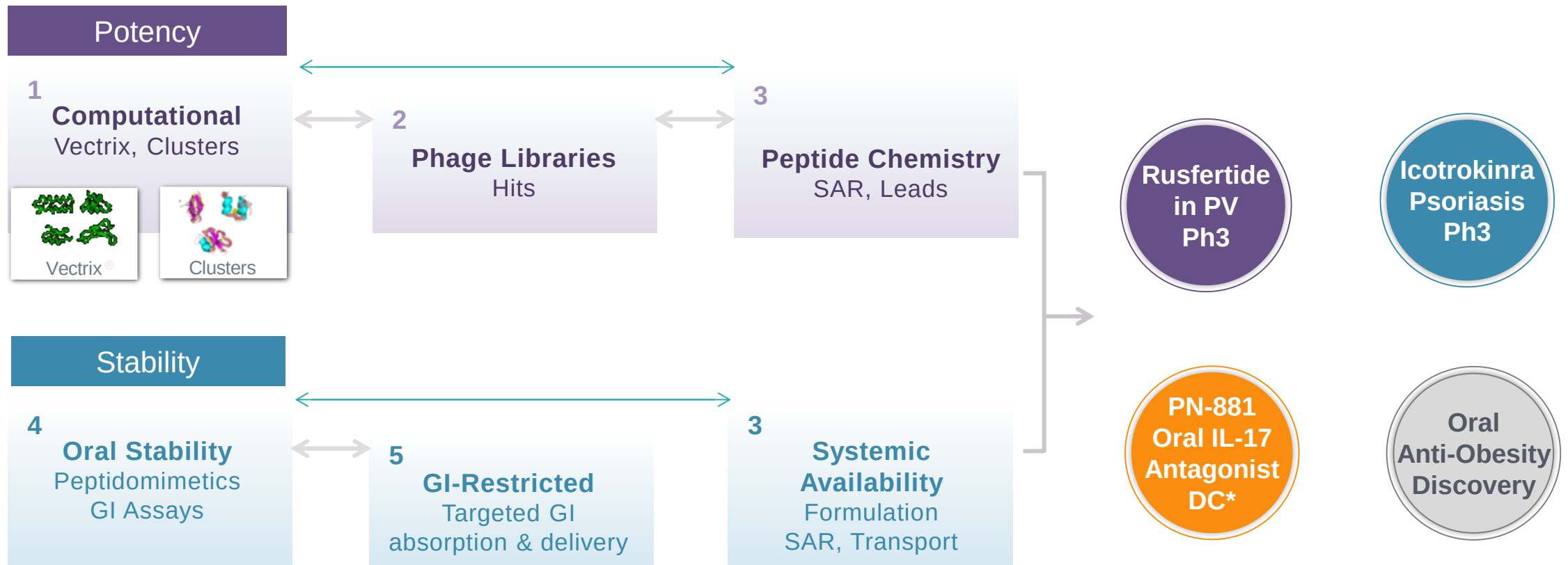
The forward-looking statements made in this presentation involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the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

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Core Competency Remains our Focus

Expertise in Peptide-based Medicines

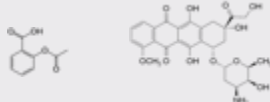
- Protagonist focuses on biologically and commercially validated targets in immunology, hematology, and metabolic diseases



Focus on Peptide-Based Medicines

Protagonist Therapeutics: Potent, Specific Peptide Therapeutics Engineered for Oral Delivery



Property	Small Molecules	Large Molecules (e.g., mAbs)	Protagonist Oral Peptides
Structure			
Potency	+	+++	+++
Specificity/Safety	+	+++	+++
Suitability For PPIs	+/-	+++	+++
Oral Stability	+++	-	+++
Oral Bioavailability	+++	-	+

Product Pipeline: Multiple Assets with Multi-Billion Dollar Market Potential

		Discovery→ Pre-Clinical→ IND-enabling	Phase 1	Phase 2	Phase 3	Key Milestones
HEMATOLOGY	  RUSFERTIDE	Polycythemia Vera (PV)				
		VERIFY Ph3, n~250				• Top-line 32-Wk Primary EP results Q1 '25
		REVIVE Ph2, n=70, 40 wk study + 3 yr OLE				• Study completed; OLE ongoing
		THRIVE Ph2 2 yr LTE, n = 46				• Ongoing; for REVIVE patients in OLE
		PACIFIC Ph2 Elevated Hct (>48%), n=20				• Completed
I & I	 Johnson&Johnson Innovative Medicine Icotrokinra (JNJ-2113) Oral IL-23R Peptide Antagonist	Psoriasis				
		FRONTIER 1 & 2 Ph2b, n = 255 & 227, in moderate-to-severe psoriasis				• Completed
		ICONIC-LEAD Ph3, n = 684, in moderate-to-severe psoriasis				• 16-Wk Primary EP achieved¹
		ICONIC-TOTAL Ph3, n=311, psoriasis in special areas of body				• 16-Wk Primary EP achieved²
		ICONIC- ADVANCE 1 Ph 3, n = 774, Icotrokinra vs. Deucravacitinib				• Preliminary results anticipated ~Q2 '25³
		ICONIC- ADVANCE 2 Ph 3, n ~731, Icotrokinra vs. Deucravacitinib				• Preliminary results anticipated ~Q2 '25⁴
		Pustular/Erythrodermic Psoriasis Ph 3, n ~19				• Preliminary results anticipated ~Q2 '25⁵
	 PN-881 Oral IL-17AA, AF, FF Peptide Antagonist	Ulcerative Colitis (UC)				
		ANTHEM-UC Ph2b, n = 252, in ulcerative colitis				• Preliminary results anticipated ~Q1 '25⁶
		Psoriasis, spondyloarthritis (SpA), and hidradenitis suppurativa (HS)				
DISCOVERY	 Discovery	Oral IL-17 antagonist ⁷				• Phase 1 initiation ~Q4 '25
		Oral Obesity				• Development candidate ~2Q '25
		Oral Hepcidin				• Development candidate ~4Q '25

¹ See [clinicaltrials.gov NCT06095115](https://clinicaltrials.gov/ct2/show/study/NCT06095115)

² See [clinicaltrials.gov NCT06095102](https://clinicaltrials.gov/ct2/show/study/NCT06095102)

³ See [clinicaltrials.gov NCT06143878](https://clinicaltrials.gov/ct2/show/study/NCT06143878)

⁴ See [clinicaltrials.gov NCT06220604](https://clinicaltrials.gov/ct2/show/study/NCT06220604)

⁵ See [clinicaltrials.gov NCT06295692](https://clinicaltrials.gov/ct2/show/study/NCT06295692)

⁶ See [clinicaltrials.gov NCT06049017](https://clinicaltrials.gov/ct2/show/study/NCT06049017)

⁷ Development Candidate: ready for IND enabling studies

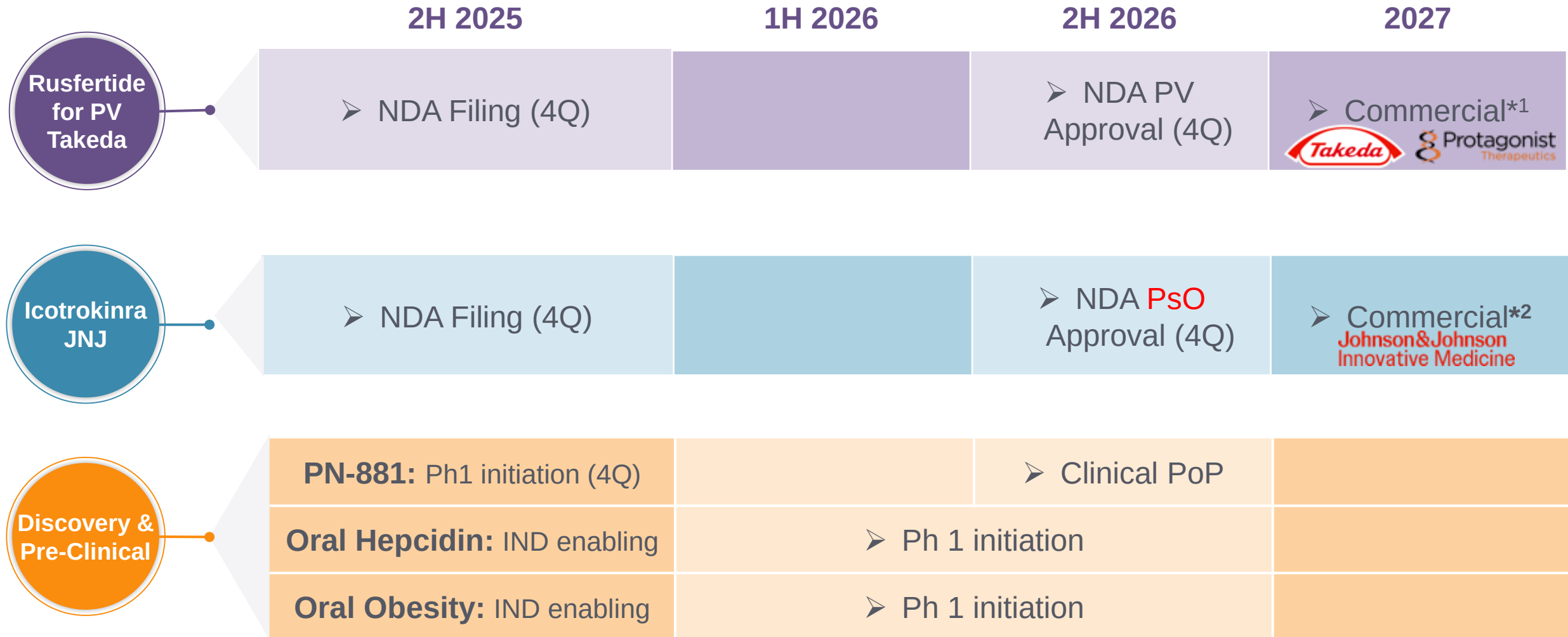
Major Upcoming Catalysts

Expected Clinical Trial Initiations, Data Readouts and Development Candidate Nominations

	Q4 2024	Q1 2025	Q2 2025	2H 2025
 Rusfertide	❖ ASH 2024	❖ Ph3 PV VERIFY		❖ NDA filing (~Q4)
 Icotrokinra	❖ Ph3 PsO LEAD ✓ ❖ Ph3 PsO TOTAL ✓	❖ Ph2b UC ANTHEM (~Q1) ❖ Ph3 PsA Initiation (~Q1) ❖ Ph3 PsO ADVANCE 1 (~Q2) ❖ Ph3 PsO ADVANCE 2 (~Q2) ❖ Ph3 PP/EP study (~Q2)		❖ NDA filing (~Q4)
 Discovery	❖ PN-881 ✓ Oral IL-17 Antagonist Development Candidate (DC)		❖ Oral Obesity DC	❖ PN-881 Ph1 (~Q4) ❖ Oral Hepcidin DC (~Q4)

Long Term Outlook: Anticipated Milestones from Now through 2027

A Transformative Path Forward for Protagonist, from Discovery to Development to Commercialization



Forecast Cash Runway And Potential Sources of Future Cash Inflows

Current financial resources extend through at least end of Q4 2028



Icotrokinra (JNJ-2113, formerly PN-235)

JNJ and Protagonist Collaboration

\$337.5M

Upfront + milestones achieved to-date

\$630M

future potential development and sales milestones

Royalty

6% to 10%

10% at ≥ \$4B net sales

Milestones Summary			Timelines
Milestones achieved in 2024			
1 st indication	Ph3 1° end point achieved	\$115M*	2024
	NDA filing	\$35M	2024
2 nd indication	Ph 3 initiation	\$15M	2024
	Total	\$165M*	
Upcoming milestones in 2026-28			Expected
1 st indication	Receipt of marketing approval	\$50M**	~2026
2 nd indication	NDA filing acceptance	\$25M**	~2027
	Receipt of marketing approval	\$45M**	~2028
	Total upcoming potential milestones	\$120M**	

*Agreement amended in November 2024 to increase \$115M to \$165M

** \$120M EXCLUDED from current cash runway forecast.

Rusfertide

Takeda and Protagonist Collaboration, 2024

**Co-development
and Co-
commercialization
partnership with
50:50 profit/loss
share in US**

- Takeda has exclusive Ex-US global rights
- Protagonist responsible for R&D through Phase 3 completion and NDA filing
- Takeda responsible for pre-commercial activities
- Up-front payment of \$300M received
- Potential 2025-26 milestones:
 - \$25M upon primary endpoint achievement in Rusfertide Phase 3 VERIFY study
 - \$50M (opt-in) or \$75M (opt-out) upon NDA approval for Rusfertide in PV

**Protagonist can
remain (OPT-IN) in
the US 50:50 profit
share, or OPT-OUT
post-NDA filing**

Scenario	Total	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	• No US profit/loss share

Financial Highlights

Financial Resources Forecast Extends Through At Least Q4 2028

CASH,
CASH EQUIVALENTS &
MARKETABLE SECURITIES

\$583.3M

as of
September 30, 2024

CASH RUNWAY
FORECAST THROUGH
AT LEAST

Q4 2028*

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

- **\$120M** in medium-term - Icotrokinra
- **\$25M** Rusfertide
- **\$50M** (or \$75M if opted-out) Rusfertide NDA approval; and
- **Up to \$400M, if** we exercise opt-out option

SHARES
OUTSTANDING

~59.5M

as of
September 30, 2024



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

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



Protagonist-Janssen Oral, IL-23R Antagonist Collaboration

Collaboration overview

- Initiated in 2017
- Icotrokinra (JNJ-2113; formerly PN-235) jointly discovered
 - Protagonist completed pre-clinical and first Ph1 study
 - JNJ responsible for further development and commercialization
- First- and best-in-class targeted oral IL-23 receptor peptide antagonist¹
- Potential peak yearly sales across indications: **\$5B+**²

Current Status of Icotrokinra

- Five Ph3 psoriasis studies ongoing
 - Once daily 200 mg dose
 - PASI 90 chosen as high bar primary endpoint for plaque psoriasis trials
 - Two head-to-head superiority studies vs. deucravacitinib
- Ph2B UC study ongoing

Icotrokinra
Oral IL-23R
Antagonist

Psoriasis (PsO)
Psoriatic Arthritis (PsA)
Ulcerative Colitis (UC)
Crohn's Disease (CD)

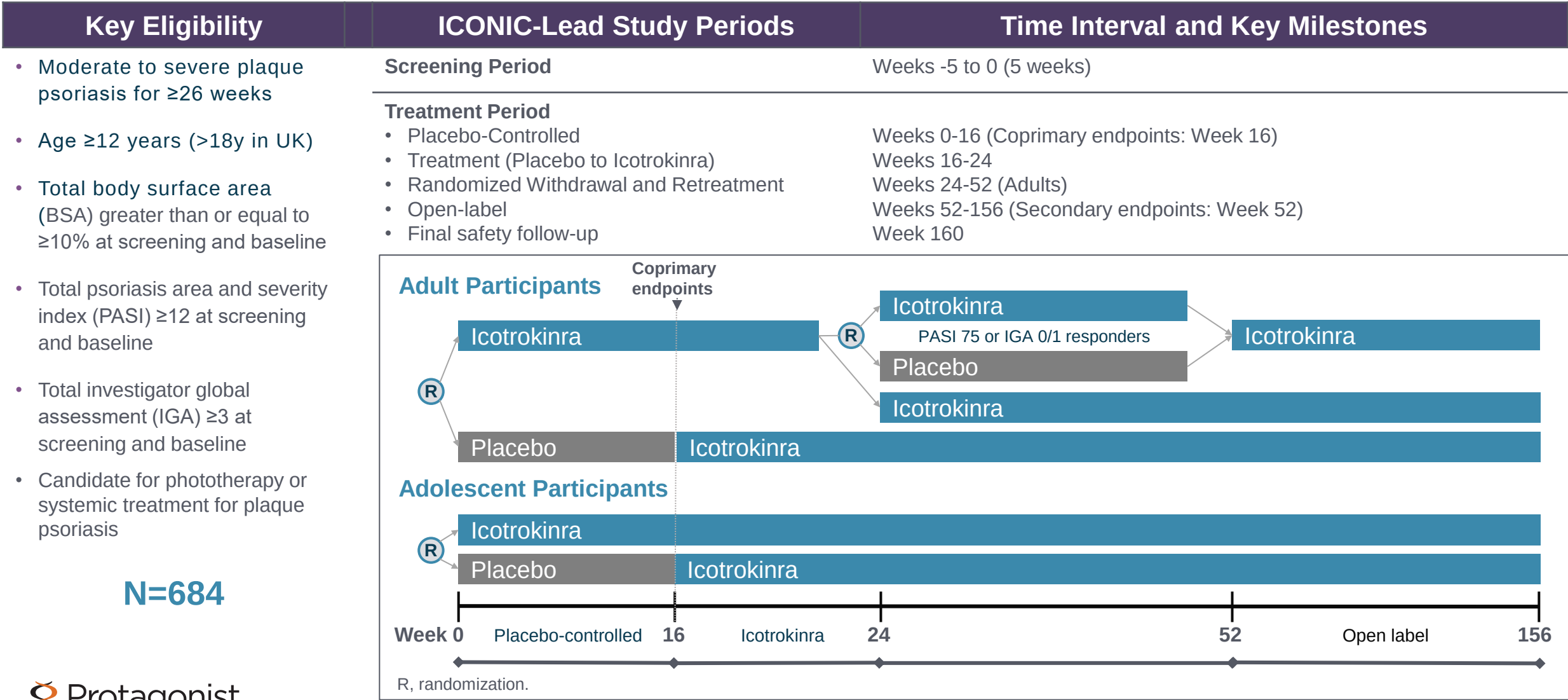
Icotrokinra (JNJ-2113): ICONIC-LEAD and ICONIC-TOTAL Phase 3 Study Results¹

Best-in-Class ORAL Targeted Therapy Potential for Psoriasis

- Icotrokinra (JNJ-2113) is a **first-in-class** and **only-in-class** oral IL-23 receptor antagonist peptide
- ICONIC-LEAD achieved its co-primary endpoints of PASI-90 and IGA of 0 or 1 at week 16
 - 74% of patients achieved clear or almost clear skin (IGA 0/1) at week 24
- ICONIC-TOTAL achieved its primary endpoint of IGA score of 0 or 1 at week 16
 - Study in patients with plaque psoriasis in difficult-to-treat areas
- Safety data were found to be consistent with the Phase 2 FRONTIER 1 and 2 studies
- Comprehensive results planned for presentation at upcoming medical congresses
- Protagonist has earned \$165 million milestone under the terms of recently amended agreement, inclusive of \$50 million in accelerated payments
 - \$115M for 1° end point achievement in a phase 3 study
 - \$35 million accelerated payment (previously due upon acceptance of an NDA in psoriasis)
 - \$15 million accelerated payment (previously due upon initiation of a phase 3 study in a 2nd indication (PsA))

Icotrekinra (JNJ-2113) Phase 3 ICONIC-LEAD Study (NCT06095115)

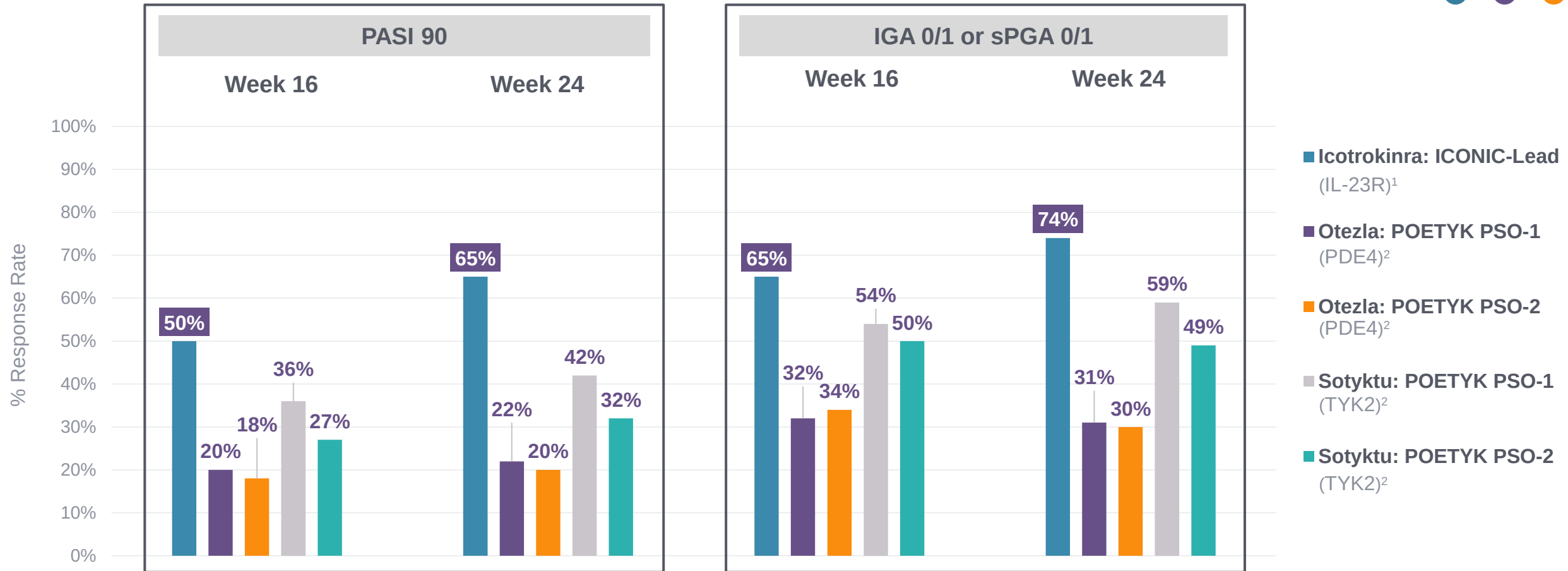
Coprimary endpoints: PASI 90 and IGA score of 0/1 with >2-grade improvement



N=684

Icotrokinra (JNJ-2113) in ICONIC-LEAD Vs Oral Approved Phase 3 Benchmarks*

Best-in-Class Oral Psoriasis Targeted Therapy Potential



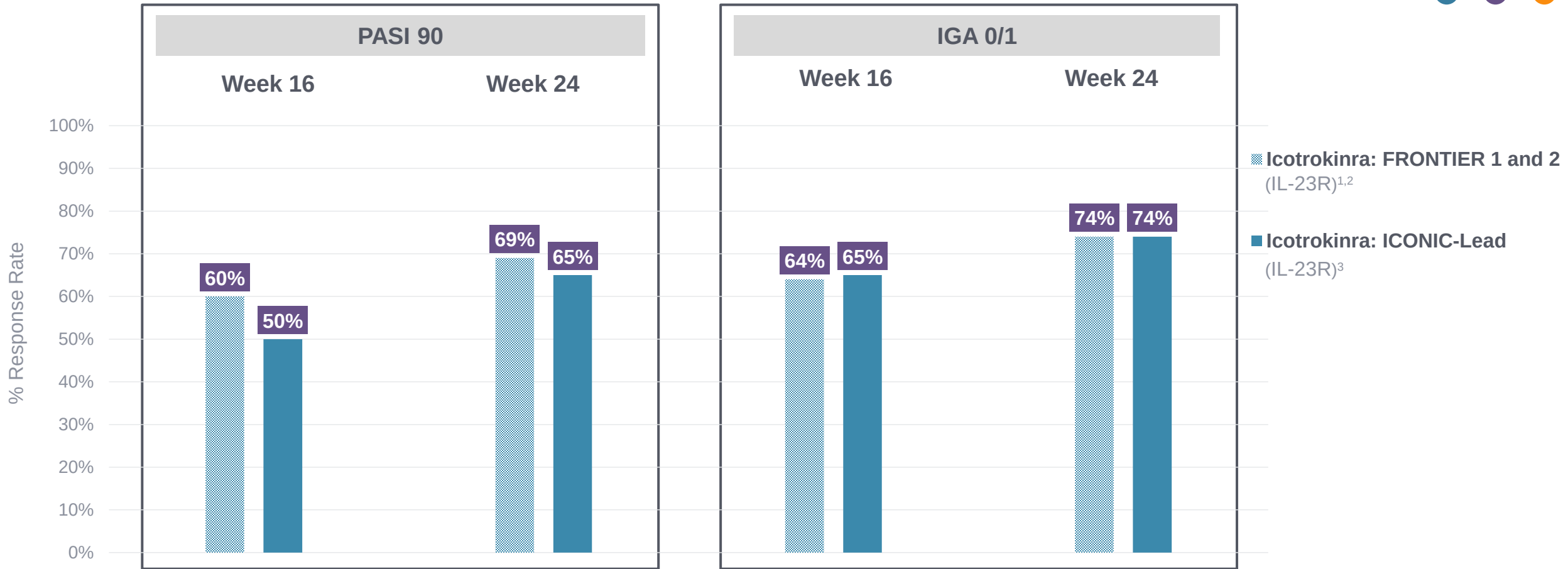
*Cross trial (not head-to-head) comparisons

1. Johnson & Johnson. "Icotrokinra delivered an industry-leading combination of significant skin clearance with demonstrated tolerability in a once daily pill in Phase 3 topline results." News release. 18 November 2024.

2. Sotyktu [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. [https://packageinserts.bms.com/pi/pi_sotyktu.pdf] September 2022. Accessed on 15 November 2024.

Icotrokinra (JNJ-2113)

Phase 3 ICONIC-LEAD vs. Phase 2 FRONTIER 1 & 2 Study Results



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

2. Ferris L, et al. Data Presentation. A Phase 2b, Long-term Extension, Dose-ranging Study of Oral JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis: FRONTIER 2. Presented at AAD, March 8-12, 2024. Abstract S026. Link to abstract [here](#).

3. Johnson & Johnson. "Icotrokinra delivered an industry-leading combination of significant skin clearance with demonstrated tolerability in a once daily pill in Phase 3 topline results." News release. 18 November 2024.

Icotrokinra (JNJ-2113) Phase 3 ICONIC-LEAD and ICONIC-TOTAL Studies¹

Summary of Safety and Efficacy Results

- Icotrokinra (JNJ-2113) is a first-in-class targeted oral peptide that selectively blocks the IL-23 receptor
- **ICONIC-LEAD:** randomized controlled trial in participants with moderate-to-severe plaque psoriasis
 - Once daily icotrokinra showed significant skin clearance versus placebo
 - At week 16,
 - nearly two-thirds (64.7%) of patients treated with icotrokinra achieved IGA scores of 0/1 (clear or almost clear skin) compared to 8.3% on placebo
 - 49.6% of patients treated with icotrokinra achieved PASI 90, compared to 4.4% on placebo
 - Further increases in response rates continued to be observed at week 24, with 74.1% of patients treated with icotrokinra achieving IGA 0/1 scores of 0/1 and 64.9% achieving PASI 90
 - Safety
 - Safety data were consistent with the Phase 2 FRONTIER 1 and 2 studies
 - The proportion of patients experiencing treatment-emergent adverse events was similar on icotrokinra and placebo (49.3% and 49.1%, respectively, at Week 16)
- **ICONIC-TOTAL:** randomized controlled trial in participants with at least moderate severity affecting special areas (e.g., scalp, genital, and/or hands and feet)
 - Once daily icotrokinra met the primary endpoint of IGA 0/1 with >2-grade improvement compared to placebo at week 16

JNJ-2113 Publication in NEJM, 2024

- Patients were randomized to doses of 25 mg qd, 25 mg bid, 50 mg qd, 100 mg qd, or 100 mg bid or placebo
- Results demonstrate a dose-dependent Psoriasis Area and Severity Index score (PASI-75) response in patients treated with JNJ-2113 versus placebo at Week 16 (primary endpoint), with 79% of patients achieving a PASI-75 response in the highest dose group (100 mg twice daily)
- Secondary endpoints results consistent with primary evaluation
 - Highest dose of JNJ-2113 showed 59.5% of patients achieving PASI-90, and 40.5% of patients achieving a PASI-100 at Week 16
 - At the highest dose, 64.3% of patients achieved an Investigator Global Assessment (IGA) score of 0/1 and 45.2% of patients achieved a score of 0, with IGA responses showing separation between JNJ-2113 and placebo groups as early as Week 4
 - Significant improvements were observed across key Patient-Reported Outcomes
- JNJ-2113 is currently being studied in
 - the ICONIC program, which includes five Phase 3 studies for moderate-to-severe psoriasis
 - ANTHEM-UC, phase 2b study in moderate-to-severe ulcerative colitis

Results of FRONTIER-1 Phase 2b Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Oral Interleukin-23–Receptor Antagonist Peptide for Plaque Psoriasis

Robert Bissonnette, M.D., Andreas Pinter, M.D., Laura K. Ferris, M.D., Ph.D.,
Sascha Gerdes, M.D., Phoebe Rich, M.D., Ronald Vender, M.D.,
Megan Miller, M.P.H., Yaung-Kaung Shen, Ph.D., Arun Kannan, Ph.D.,
Shu Li, Ph.D., Cynthia DeKlotz, M.D., and Kim Papp, M.D., Ph.D.

Key Presentations and Publications: Icotrokinra (JNJ-77242113; in descending order by date)

Manuscripts:

- Fourie AM, Cheng X, Chang L, et al. JNJ-77242113, a highly potent, selective peptide targeting the IL-23 receptor, provides robust IL-23 pathway inhibition upon oral dosing in rats and humans. Sci Rep. 2024;14(1):17515. Link to manuscript [here](#).
- Bissonnette R, Pinter A, Ferris LK, et al. An Oral Interleukin-23-Receptor Antagonist Peptide for Plaque Psoriasis. N Engl J Med. 2024;390(6):510-521. Link to manuscript [here](#).

Abstracts and Presentations:

- Ferris L, Bagel J, Huang Y, et al. Phase 2b, Long-term Extension, Dose-ranging Study of Oral JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis: FRONTIER-2 [abstract]. Arthritis Rheumatol. 2024; 76 (suppl 9). Link to abstract [here](#).
- Ferris L, et al. Data Presentation. A Phase 2b, Long-term Extension, Dose-ranging Study of Oral JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis: FRONTIER 2. Presented at AAD, March 8-12, 2024. Abstract S026. Link to abstract [here](#).
- Armstrong, AW, Ferris L, Gerdes S, et al. Data Presentation. 53750 Improvements in Patient-Reported Symptoms and Signs of Moderate-to-Severe Psoriasis With JNJ-77242113: Results of the FRONTIER 1 Study. J Am Acad Dermatol. 2024;91(3): AB236. Link to abstract [here](#).
- Papp KA, Ferris L, Pinter A, et al. Data Presentation. 54112 Improvements in Psoriasis Area and Severity Index and in Percent Body Surface Area of Psoriasis With JNJ-77242113: Treat-to-Target Analyses in the FRONTIER 1 Study. J Am Acad Dermatol. 2024;91(3): AB53. Link to abstract [here](#).
- Pinter A, Eyerich K, Paller A, et al. Data Presentation. JNJ-77242113 Treatment Induces a Strong Systemic Pharmacodynamic Response Versus Placebo in Serum Samples of Patients with Plaque Psoriasis: Results from the Phase 2, FRONTIER 1 Study. Presented at EADV, October 11-14, 2023. Abstract 810. Link to abstract [here](#).
- Bissonnette R, Pinter A, Ferris L, et al. Data Presentation. A phase 2, randomized, placebo-controlled, dose-ranging study of oral JNJ-77242113 for the treatment of moderate-to-severe plaque psoriasis: FRONTIER 1. Presented at 25th WCD, July 3-8, 2023. Late-breaking abstract LB01. Link to abstract [here](#).
- Fourie A, Cheng X, Chang L, et al. Data Presentation. 1109. First-in-class oral peptide systemically targeting the IL-23 pathway. J Invest Dermatol 2023;143(Suppl: S190). Link to abstract [here](#).

Ichotrokinra (JNJ-2113) Market Potential¹

Big Opportunity for a safe and effective oral, once daily medication

- **50-70%** of patients (~5 million in G8) living with psoriatic and IBD conditions and are eligible for advanced therapies, and yet aren't receiving them

Reasons eligible patients avoid using advanced treatments²

30% Method of administration

75% Overall risk/benefit profile

Market growth expected to be driven by orals⁴

Patients on injectables who would switch to an oral with similar safety & efficacy³

75%

~5M Eligible patients not receiving advanced therapy

Growing Market for Oral Treatment Options⁵

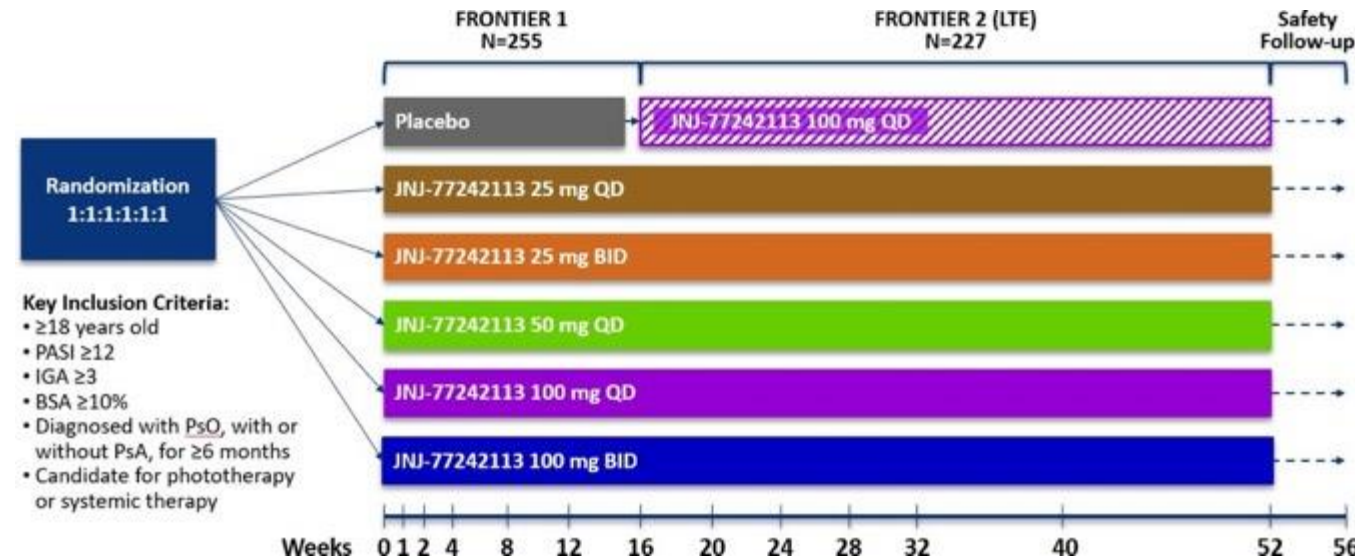
WW market Size 2030 est. (7-yr CAGR) ¹	PsO	~\$35B (4-6%)
	PsA	~\$8B (4-6%)
	CD	~\$19B (2-4%)
	UC	~\$13B (7-9%)

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

Icotrokinra (JNJ-2113) FRONTIER 2 Long-term Extension, Dose-Ranging Study

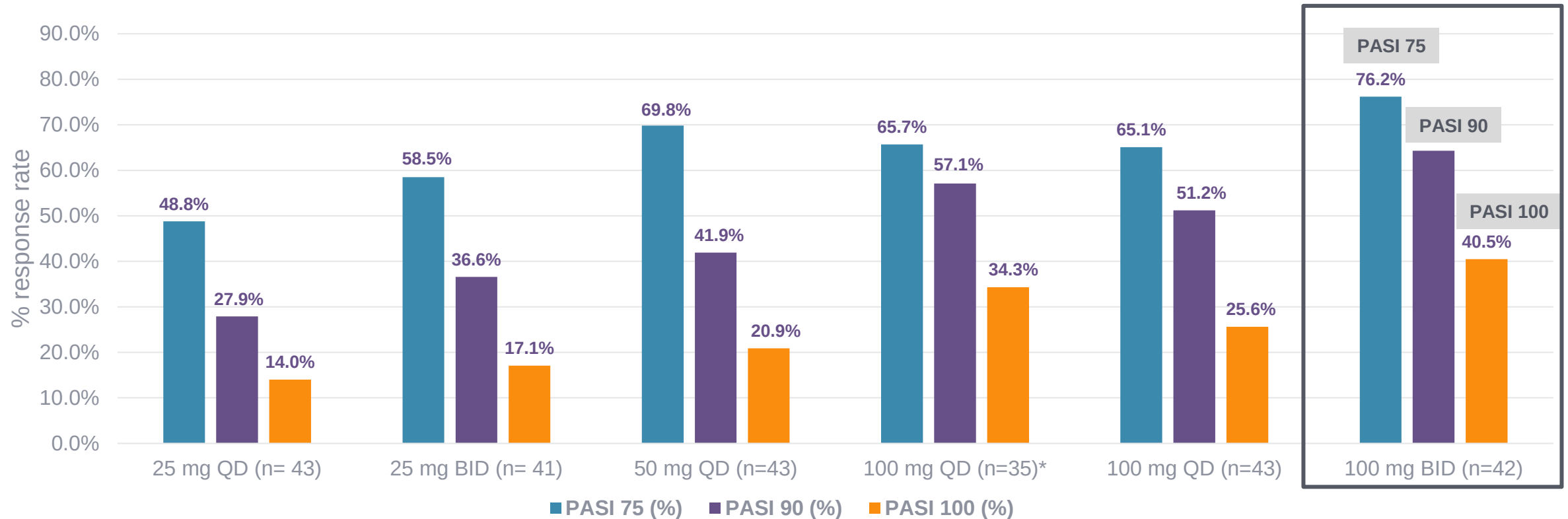
Study Design and Methods

- In FRONTIER 2, patients randomized to a JNJ-77242113 dosing group in FRONTIER 1 continued treatment through Week 52
- Patients from the FRONTIER 1 PBO group crossed over to JNJ-77242113 100 mg daily (QD) at Week 16 (PBO→100 mg QD)
- Efficacy endpoints (dichotomous and continuous endpoints utilized NRI and MMRM, respectively):
 - All JNJ-77242113-randomized patients
 - 35 PBO →100 mg QD patients
 - Scalp-specific Investigator's Global Assessment (ss-IGA): assessed in patients with an ss-IGA ≥ 2 at baseline
- Adverse events: assessed in patients who entered the LTE and received ≥ 1 dose of JNJ-77242113 treatment



Icotrokinra (JNJ-2113) Phase 2B Frontier 2 Data – Week 52

Dose Response



- PASI-75, -90, and -100 rates were generally maintained from week 16 through week 52

* Patients who crossed over from PBO→100 mg QD at Week 16

Patients who discontinued study agent due to lack of efficacy/worsening of PsO, or who initiated a prohibited PsO treatment were considered non-responders after the occurrence. Patients with missing data were considered non-responders.

2024 EADV Meeting (Amsterdam, The Netherlands; 25-28 September)

Icotrokinra (JNJ-2113) Featured in Four Company-Sponsored Oral/Poster Presentations

- Three company-sponsored poster presentations and one company-sponsored oral presentation was delivered at the 2024 EADV Meeting (Amsterdam; 25-28 September)¹⁻⁴
 - Data from FRONTIER 1 and 2 continue to demonstrate that JNJ-2113 has promising efficacy and safety through 1 year of treatment in patients with moderate-to-severe plaque PsO¹
 - At Week 52, the highest response rate was achieved in the 100 mg BID dosing group for JNJ-2113¹
 - **97% of all JNJ-2113 100 mg BID treated patients indicated being somewhat-to-extremely satisfied with treatment medication at Wk52²**
 - Satisfaction in symptom relief correlated with reduction in physician and patient-reported measures of disease activity at Wk16²
 - Sustained satisfaction with JNJ-2113 effectiveness may reflect the previously reported durable rates of nearly complete or complete skin clearance in these patients²
 - **High rates of clinically meaningful improvement in PsO symptoms & signs at Wk 16 maintained through Wk 52³**
 - **Rapid *itch* and *pain* relief; high rates of Clinically meaningful improvement were maintained³**
 - These preliminary findings will be confirmed in ongoing Phase 3 studies
 - **Treatment with JNJ-2113 provided robust and sustained skin improvements⁴**
 - Sustained improvements in psoriasis area, severity index, and in percent body surface area of psoriasis

CMI, clinically meaningful improvement; NRI, non-responder imputation; PsO, psoriasis.

1. Ferris LK, et al. Poster ID **P3105**. Presented at the 2024 EADV Meeting, Amsterdam

2. Ferris LK, et al. Poster ID **P3144**. Presented at the 2024 EADV Meeting, Amsterdam;

3. Armstrong AW, et al. Oral Presentation, FC06.09. Presented at the 2024 EADV Meeting, Amsterdam

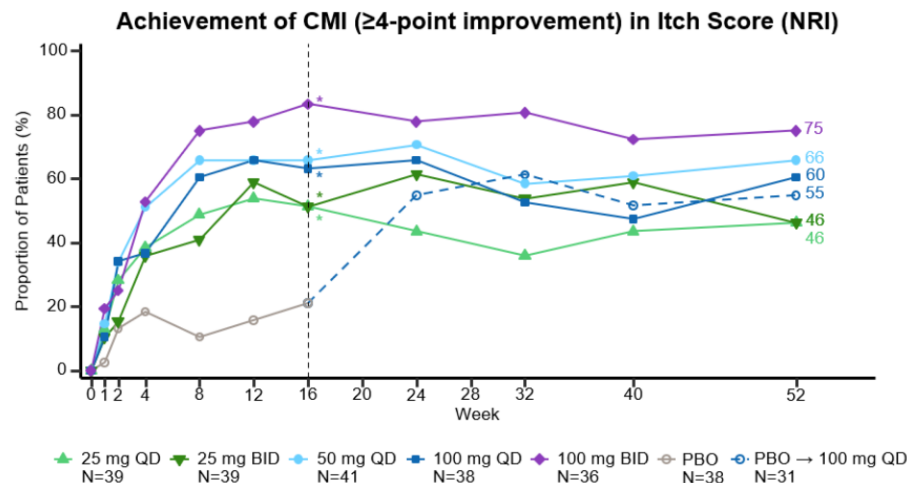
4. Papp KA, et al. Poster ID **P3092**. Presented at the 2024 EADV Meeting, Amsterdam

2024 EADV Meeting (Amsterdam, The Netherlands; 25-28 September)

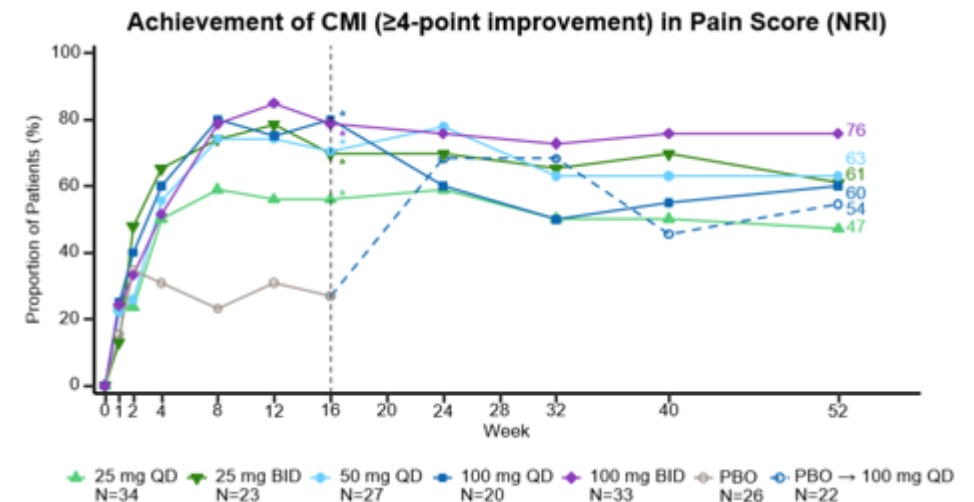
High Rates of Clinically meaningful improvement in Psoriasis Symptoms and Signs with JNJ-2113



✓ JNJ-2113 provided rapid *itch* relief; high rates of CMI were maintained³



✓ JNJ-2113 provided rapid *pain* relief; high rates of CMI were maintained³



These preliminary findings will be confirmed in ongoing phase 3 studies in psoriasis

Icotrokinra (JNJ-2113) FRONTIER 2 Long-term Extension, Dose-Ranging Study

Safety Summary



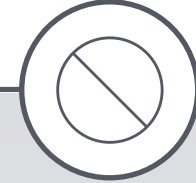
- 59% experienced ≥ 1 AEs
- Rates of GI-related AEs did not increase in patients receiving JNJ-77242113 during the LTE (6% JNJ-77242113 combined group)
- FRONTIER 1 Week 16: 12% PBO vs 11% JNJ-77242113 combined group



- The most common AEs were nasopharyngitis (18.1%), upper respiratory tract infection (9.7%), and COVID-19 (5.3%)
- No evidence of dose-dependent increase in the occurrence of AEs



- 4% experienced serious AEs through Week 52
- All serious AEs were considered not related to study intervention by investigators



- No deaths occurred during the LTE

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

Adult Patients with UC

N = 252

Eligibility:

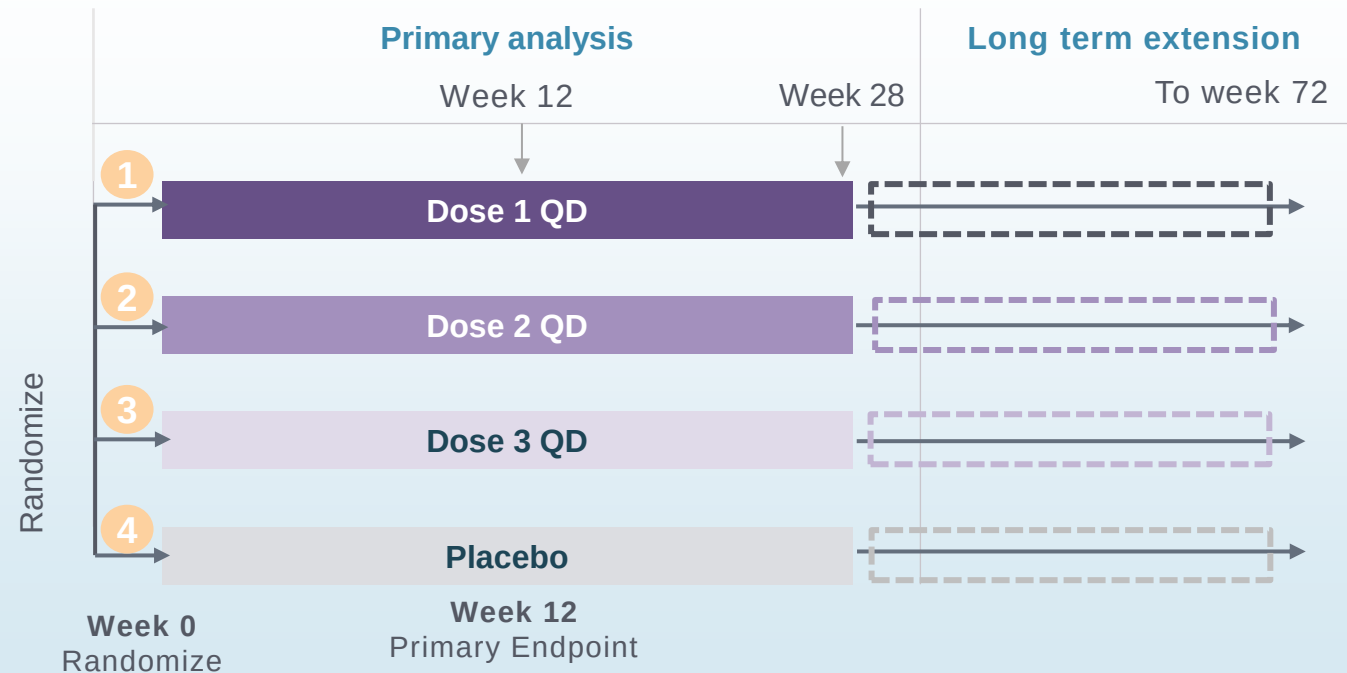
- 18 years of age or older
- Moderately to severely active UC as per the modified Mayo score
- Demonstrated inadequate response to or intolerance of conventional therapy and/or advanced therapy

Primary endpoint:

- Clinical Response (Modified Mayo score) at Week 12

Study Start: 10/9/23

Estimated Primary Completion: 5/27/25



- Enrollment completed
- Primary endpoint completion ~September 2024

Rusfertide

Hepcidin Hormone Mimetic

Addressing Unmet Needs in
Polycythemia Vera



Rusfertide Publication in *NEJM*, 2024¹

- Phase 2 REVIVE study investigating rusfertide in PV published in *The New England Journal of Medicine* on 21 February 2024
- REVIVE met the primary efficacy endpoint and achieved a clinically and statistically significant response in maintaining hematocrit control <45%
- Rusfertide associated with lower disease-related symptoms in patients with moderate to severe symptoms at baseline (assessed by the MPN-SAF)
- Most common adverse events were grade 1-2 injection site reactions; no grade 4 or 5 adverse events were reported
- Phase 3 VERIFY study is ongoing to evaluate rusfertide in patients with PV

Results of REVIVE Phase 2 Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera

M. Kremyanskaya, A.T. Kuykendall, N. Pemmaraju, E.K. Ritchie, J. Gotlib, A. Gerds, J. Palmer, K. Pettit, U.K. Nath, A. Yacoub, A. Molina, S.R. Saks, N.B. Modi, F.H. Valone, S. Khanna, S. Gupta, S. Verstovsek, Y.Z. Ginzburg, and R. Hoffman, for the REVIVE Trial Investigators*

¹Kremyanskaya et al. *New Engl J Med*;2024;390:723-35.

Key Presentations and Publications: Rusfertide (in descending order by date)

Manuscripts:

- Modi NB, Shames R, Lickliter JD, et al. Pharmacokinetics, pharmacodynamics, and tolerability of an aqueous formulation of rusfertide (PTG-300), a hepcidin mimetic, in healthy volunteers: A double-blind first-in-human study. *Eur J Haematol*. 2024;113(3):340-350. Link to manuscript [here](#).
- Kremyanskaya M, Kuykendall AT, Pemmaraju N, et al. Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera. *N Engl J Med*. 2024;390(8):723-735. Link to manuscript [here](#).
- Kowdley KV, Modi NB, Peltekian K, et al. Rusfertide for the treatment of iron overload in HFE-related haemochromatosis: an open-label, multicentre, proof-of-concept phase 2 trial. *Lancet Gastroenterol Hepatol*. 2023;8(12):1118-1128. Link to manuscript [here](#).

Abstracts and Presentations:

- Modi N, Rudraraju S, Dinh P, et al. Data Presentation. Pharmacokinetics, Pharmacodynamics and Safety of Rusfertide, a Hepcidin Mimetic, in Subjects With Hepatic Impairment and in Subjects With Renal Impairment. *Clin Pharmacol Drug Dev*. 2024;13(S1):72-73. Link to abstract [here](#).
- Modi N, Dinh P, Xue H, et al. (PB2872) Absence of QTc prolongation with rusfertide, a hepcidin mimetic for the treatment of polycythemia vera: a thorough QT/QTc study in healthy subjects. *HemaSphere*, 2024;8:(S1):5365-5366. Link to abstract [here](#).
- Pettit K, Kuykendall A, Ritchie E, et al. Data Presentation. (S218) Updated Long-Term Results From the Phase 2 REVIVE Study Investigating the Hepcidin Mimetic Rusfertide in Polycythemia Vera Patients (Pts): Hematocrit Control and Therapeutic Phlebotomy (TP) Frequency. *HemaSphere*, 2024;8:(S1):252-253. Link to presentation [here](#); link to abstract [here](#).
- Ritchie EK, Pettit KM, Kuykendall AT, et al. Data Presentation. Durability of Hematocrit Control in Polycythemia Vera with the First-in-Class Hepcidin Mimetic Rusfertide: Two-Year Follow up Results from the REVIVE Study. *Blood*. 2023;142 (Supplement 1): 745. Link to presentation [here](#); link to abstract [here](#).
- Ginzburg Y, Chew LP, Modi N, et al. Data Presentation. Rusfertide Improves Markers of Iron Deficiency in Patients with Polycythemia Vera. *Blood*. 2023;142 (Supplement 1): 3208. Link to presentation [here](#); link to abstract [here](#).
- Kremyanskaya M, et al. Data Presentation. Targeted Therapy of Uncontrolled Erythrocytosis in Polycythemia Vera With the Hepcidin Mimetic, Rusfertide: Blinded Randomized Withdrawal Results of the REVIVE Study. Presented at the 2023 EHA Meeting, June 8-15, 2023. Late-breaking abstract LB2710. Link to presentation [here](#); link to abstract [here](#).
- Kremyanskaya M, Chew LP, Rudraraju S, et al. Data Presentation. P1048. Pharmacokinetic and Pharmacodynamic Effects of Rusfertide in Polycythemia Vera: Results From an Ongoing Phase 2 Study in Patients With Elevated Hematocrit Values. *HemaSphere*, 2023;7:(S3):2007-2008. Link to abstract [here](#).
- Pemmaraju N, Verstovsek S, Kremyanskaya M, et al. Data Presentation. Subgroup Analysis of Adverse Events Following Rusfertide Dosing in REVIVE: A Phase 2 Study of Patients with Polycythemia Vera. *Blood*. 2022; 140 (Supplement 1): 6835–6837. Link to presentation [here](#); link to abstract [here](#).
- Gerds AT, Gotlib J, Palmer JM, et al. Data Presentation. Rusfertide for Polycythemia Vera: Similar Dosing in Patients Receiving Therapeutic Phlebotomy Alone or in Combination with Cytoreductive Treatment. *Blood*. 2022;140 (Supplement 1): 12241–12243. Link to abstract [here](#).
- Verstovsek S, Kuykendall AT, Hoffman R, et al. Data Presentation. A Phase 3 Study of the Hepcidin Mimetic Rusfertide (PTG-300) in Patients with Polycythemia Vera. *Blood*. 2021;138 (Supplement 1): 1504. Link to presentation [here](#); link to abstract [here](#).
- Ginzburg Y, Kirubamoorthy K, Salleh S, et al. Data Presentation. Rusfertide (PTG-300) Induction Therapy Rapidly Achieves Hematocrit Control in Polycythemia Vera Patients without the Need for Therapeutic Phlebotomy. *Blood*. 2021;138 (Supplement 1): 390. Link to presentation [here](#); link to abstract [here](#).

Polycythemia Vera

Disease Background

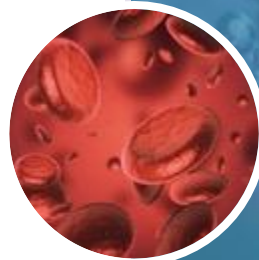
Myeloproliferative neoplasm characterized by excessive production of red blood cells (RBCs)¹

- Elevated hematocrit (Hct) is a hallmark of the disease, indicating overproduction of RBCs²

Serious, chronic disease associated with increased thrombotic and cardiovascular risks¹⁻³

Rare disease with ~100,000 diagnosed and treated patients in US¹

- Diagnosed commonly in individuals 50-70 years of age
- Median survival ~20 years



Treatment goal is to control

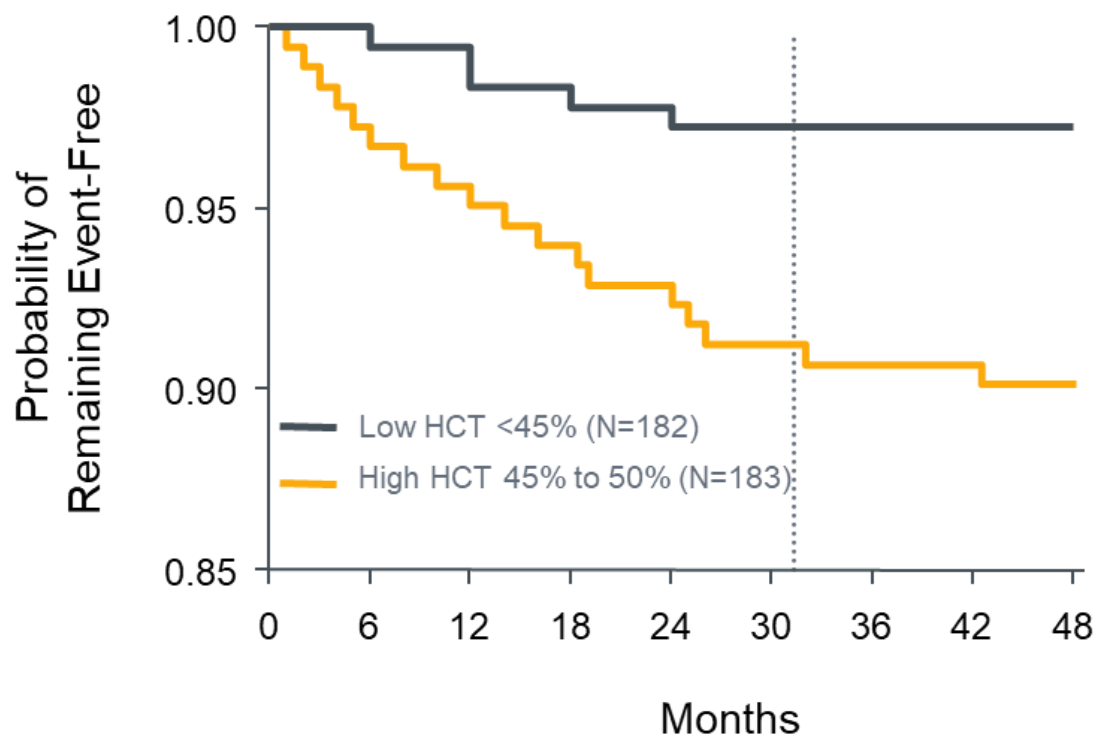
HCT < 45%

to minimize TEs, CV events and death³

Increased Hematocrit is Associated with Increased Morbidity and Mortality

Current Treatment Options are Inadequate

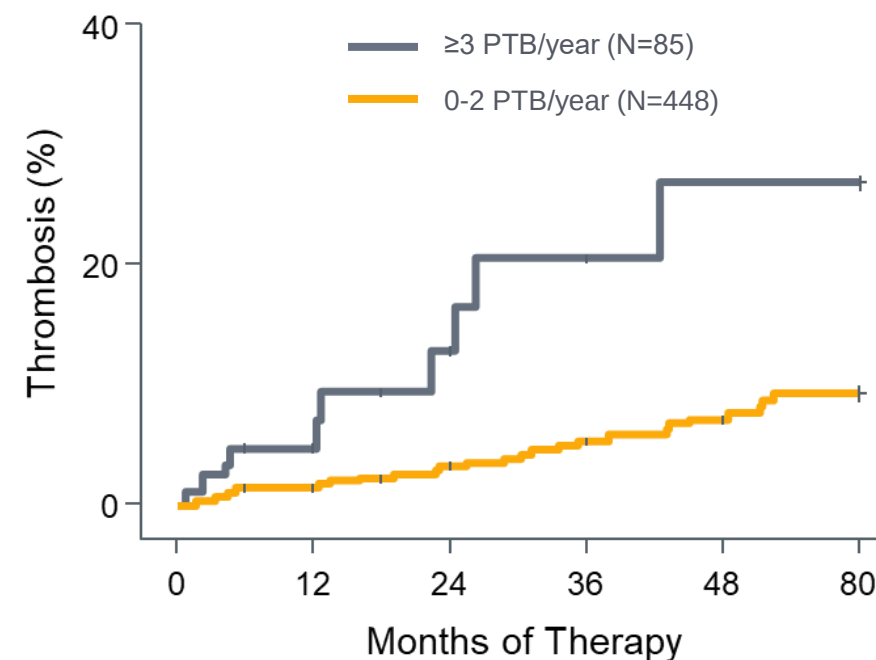
Elevated Hematocrit Contributes to ~4x Increased Risk of CV Death and Major Thrombosis



Marchioli, R. et al., *N Engl J Med.* 2013;368(1):22-33.

Phlebotomy, Even with Concomitant Cyto-reductive Therapy, Is Inadequate in Reducing Thrombotic Risk

All HU-treated ($P<0.0001$)



Alvarez-Larran et al. *Haematologica* 2017; 102:103-109

Thromboembolic Events are Associated with PV

- In observational studies, **patients with PV had higher rates of TEs** compared to matched controls (14.3 vs 4.9/1000 patient years)¹⁻³
- In a retrospective analysis of US electronic health records contained in the Optum® MarketClarity database, TEs were evaluated in 20,000+ PV patients (date range: 2007-2019)⁴
 - Approximately **25% of PV patients experienced post-index TEs**
 - TE incidence was highest among event-based high-risk patients (50.2%), followed by age-based high-risk (25.0%) and low-risk patients (13.3%)

Parameter	Total cohort	Event-based high-risk	Age-based high-risk	Low-risk
Total	N=20,089	n=3,256	n=9,924	n=6,909
Any TE, n (%)	5,035 (25.1)	1,634 (50.2)	2,480 (25.0)	921 (13.3)

- In PV patients with 5 years of follow-up data, high-risk patients had a greater risk of death than event-based low risk patients (37% vs 8.5%, respectively)
- **These data suggest that thrombotic risk reduction should be an area of focus across all PV risk groups**

Prevalence of Second Cancers in PV

Second Cancers

- One large population-based study found that **patients with MPNs had a 60% higher risk of developing second non-hematologic cancers** compared to matched controls¹
 - **Skin cancers were among the most prevalent second cancers** (2.8-fold increase in risk of non-melanoma skin cancer vs. matched controls)
- In a retrospective analysis of US electronic health records contained in the Optum® Market Clarity database, the post-index period prevalence of second cancers was evaluated in 20,000+ PV patients (date range: 2007-2019)²
 - **35.7%** of patients had **at least one second cancer** in the post-index period; **the highest rates were observed for skin cancers**
 - **9.1%** of patients had **any form of skin cancer**
 - **8.3%** of patients had **non-melanoma skin cancer**
 - **1.4%** of patients had **melanoma**
 - Patients treated with hydroxyurea had nearly **2×** the rate of skin cancers compared to patients treated with phlebotomy alone
- **Given these data^{1,2}, patients with PV appear to have high rates of second cancers, including skin cancers**

The Unmet Need in PV is Three-Fold

Inconsistent Hct Control, Iron Deficiency, and Symptom Burden

Inconsistent Hct Control



- Maintaining Hct <45% is critical, as uncontrolled Hct is associated with ~4 times higher rate of death from cardiovascular causes or thrombotic events²
- Real-world data shows that 78% of patients have uncontrolled Hct with tests $\geq 45\%$ ¹

Iron Deficiency



- Most patients with PV are iron deficient due to depleted bone marrow iron levels³
- Some treatments exacerbate disease-related symptoms by inducing iron deficiency^{3,4}
- There is no pharmaceutical option with RBC-specific mechanism

Symptom Burden



- Patients have burdensome symptoms, including fatigue and concentration problems⁵
- 84% of patients report fatigue, and 23% report spending full days in bed because of symptoms⁶
- PV impacts reported activities of daily living and productivity⁵

Hydroxyurea is the Gatekeeper to Other Agents in PV

» HU, used alone or in combination with phlebotomy, is the most common 2nd and 3rd line PV therapy¹

- » Many patients require high doses of HU, but still experience inadequate Hct control
- 60% of patients receiving HU require $\geq 1,000\text{mg}$ daily¹
 - 35% of patients receiving HU experience Hct $\geq 45\%$ ²
 - Some patients may be intrinsically resistant to HU, making even high doses $\geq 2,000\text{mg}$ ineffective²

- » HU is associated with potentially serious side effects and adverse events³
- Myelosuppression may lead to anemia, leukopenia, and thrombocytopenia, especially at high doses
 - Long-term use of HU can cause secondary leukemias and skin cancers

Sub-optimal efficacy and safety of HU illustrates an unmet need for PV patients with elevated Hct that cannot be managed without frequent phlebotomies

Marketed Agents for PV are Cyto-reductive 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 PV¹

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 study³

Black box warning for serious neuropsychiatric, autoimmune, ischemic, and infectious disorders²



Ruxolitinib

Jakafi®

Only approved for hydroxyurea-resistant or intolerant patients⁴

Improves splenomegaly, a potential marker of disease progression⁵

Potential serious side effects include thrombocytopenia, neutropenia, and anemia⁴

23% of patients were found to have discontinued ruxolitinib within a mean of **2 years** post treatment initiation⁶

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 $\leq$ 45%

Frequent phlebotomies may exacerbate iron deficiency and related symptoms¹

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 malignancies²

Thrombotic Events

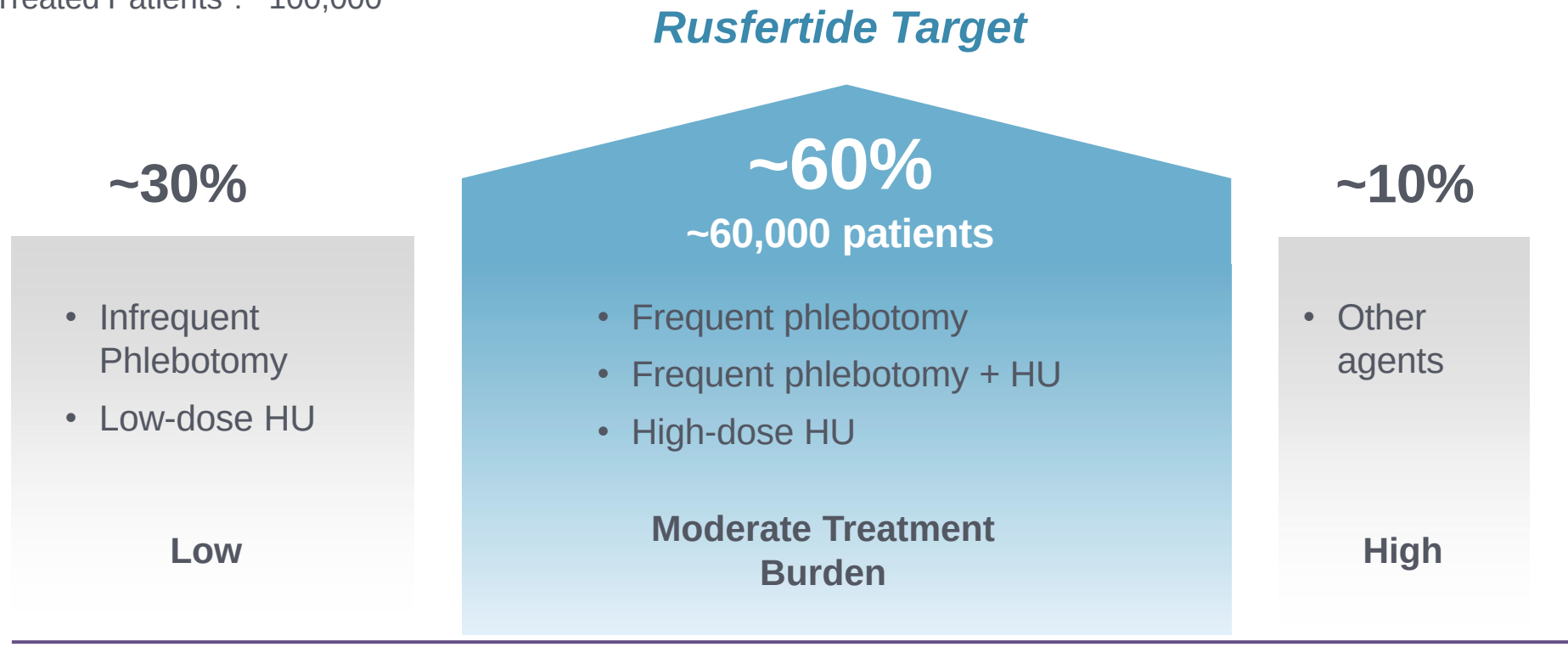


Occurrence of thrombotic events following treatment initiation can be an indicator of the ineffectiveness of the treatment – an example of a sub-optimally controlled PV patient

Potential Commercial Positioning for Rusfertide

Potential Therapy of Choice for Patients with Moderate Treatment Burden

Prevalent Patients in US¹: ~160,000
Diagnosed & Treated Patients²: ~100,000



Rusfertide for Polycythemia Vera

Successful Phase 2 Completion and Phase 3 Enrollment Completion

- Phase 2 **REVIVE** Study (n=70):
 - Randomized withdrawal data presented at EHA 2023¹ (late-breaking oral presentation); data published in *NEJM*²
 - Full Analysis Population: 69% responder rate (vs. 19% placebo; p=0.0003)
 - Randomized Population: 60% responder rate (vs. 17% placebo; p=0.002)
 - Long-term extension data presented at ASH 2023³ and EHA 2024;⁴ final data to be presented at ASH 2024
 - Durable hematocrit control through 3+ years
- Phase 2 **THRIVE** Study (n≈50):
 - Long-term extension study (for REVIVE patients on study years 3-5)
- Phase 2 **PACIFIC** Study (n=20)⁵:
 - High hematocrit (Hct >48%); 52-week open-label study completed in Q2 2023
- Phase 3 **VERIFY** Study (n≈250)⁶:
 - Enrollment completed 1Q 2024
 - Primary endpoint essentially same as phase 2; statistical powering geared for proving secondary endpoints
 - Secondary endpoints include multiple instruments that measure patient symptoms (i.e., patient reported outcomes)

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

Phase 3 Study **VERIFY** (NCT05210790)

Rusfertide vs Placebo in Patients With Polycythemia Vera

Key Eligibility Criteria:

- Age ≥18 years
- Meet revised 2016 WHO criteria for diagnosis of PV
- ≥3 phlebotomies due to inadequate Hct control in 28 weeks before randomization OR ≥5 phlebotomies due to inadequate Hct control within 1 year prior to randomization
- Use of therapeutic phlebotomy with or without CRT is permitted. Patients who receive CRT at randomization must be on a stable CRT (i.e., CRT dose increases during Parts 1a and 1b are not permitted)

CRT, cytoreductive therapy; Hct, hematocrit; PV, polycythemia vera.



Part 1A: Double-Blind

Dose Titration Period (Weeks 0-20)

- Rusfertide or placebo added to ongoing PV therapy at time of randomization

Primary Efficacy Endpoint (Weeks 20-32)

- Proportion of patients achieving response (defined as absence of phlebotomy eligibility)*

*Phlebotomy eligibility defined as either (1) confirmed Hct ≥45% and that is ≥3% (absolute) higher than the baseline Hct; or (2) Hct >48%

Part 1B: Open-Label

Durability of Response** (Weeks 32-52)

- Open-label treatment phase during which all patients who complete Part 1a successfully will receive rusfertide for 20 weeks (Weeks 32 through 52)

**Parts 1a and 1b combined will be utilized to evaluate rusfertide's durability of response over 52 weeks

Rusfertide + phlebotomy ± CRT

Rusfertide + PV therapy

Placebo + phlebotomy ± CRT

Rusfertide + PV therapy

After completing Part 1b, patients are eligible to continue receiving rusfertide for an additional two years (Part 2; study Weeks 52 to 156; long-term safety assessment)



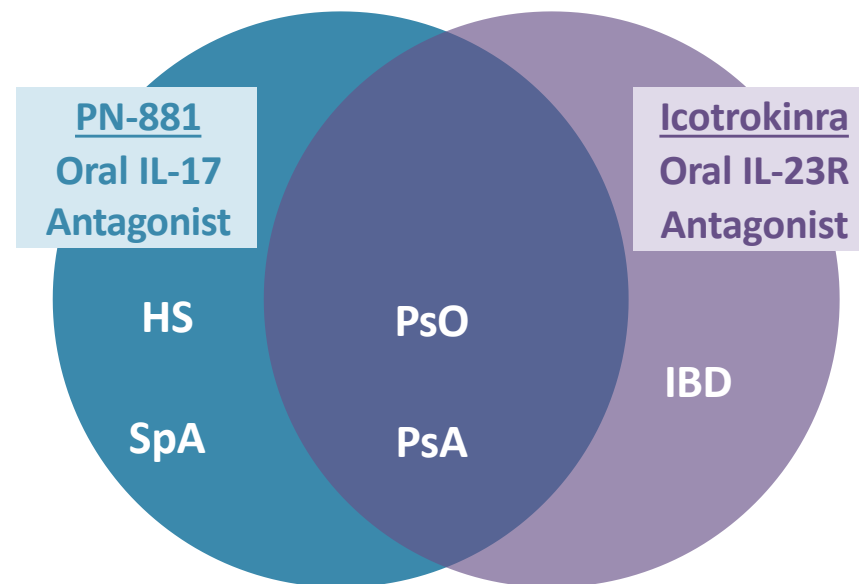
PN-881:
Oral Peptide IL-17 Antagonist
Development Candidate



Oral IL-17 Peptide Antagonist Program

Nomination of PN-881 as a Development Candidate

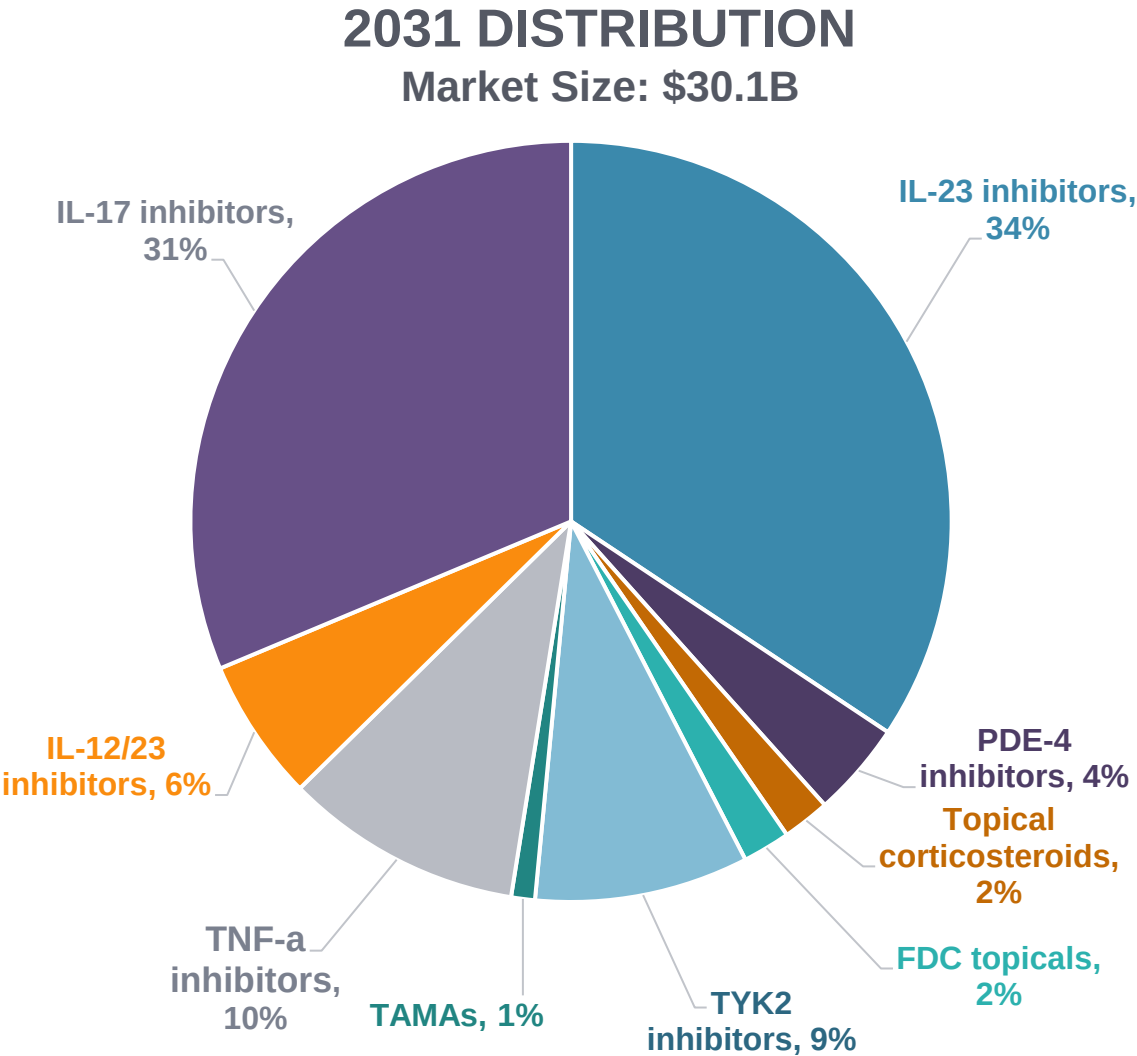
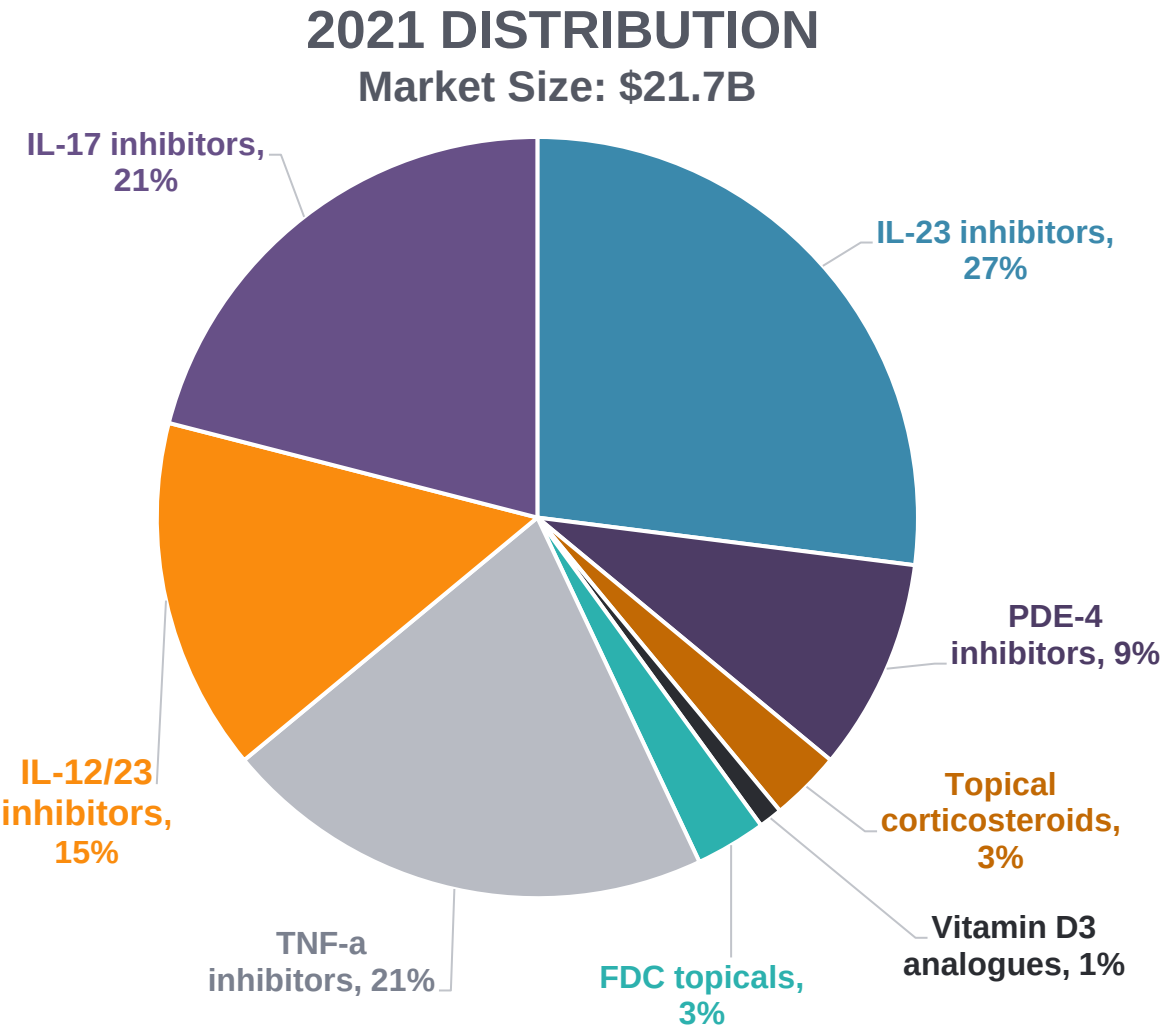
- IL-17 is a clinically validated target in psoriasis, PsA, HA, and AS/nrSpA and provides a significant commercial opportunity¹:
 - IL-17s are expected to capture 31% of the PsO market by 2031, generating \$9.3B
 - In PsA, HS, and AS/nrSpA, growth of IL-17 antagonists is anticipated to result in additional sales of \$7.7B by 2034
- Leveraging our oral peptide technology platform, we have identified a development candidate²: **PN-881**
- Differentiated target product profile (TPP)
 - Potential for best-in-class oral peptide
 - Specificity for IL-17A and IL-17F ligands (IL-17 AA, AF & FF)³



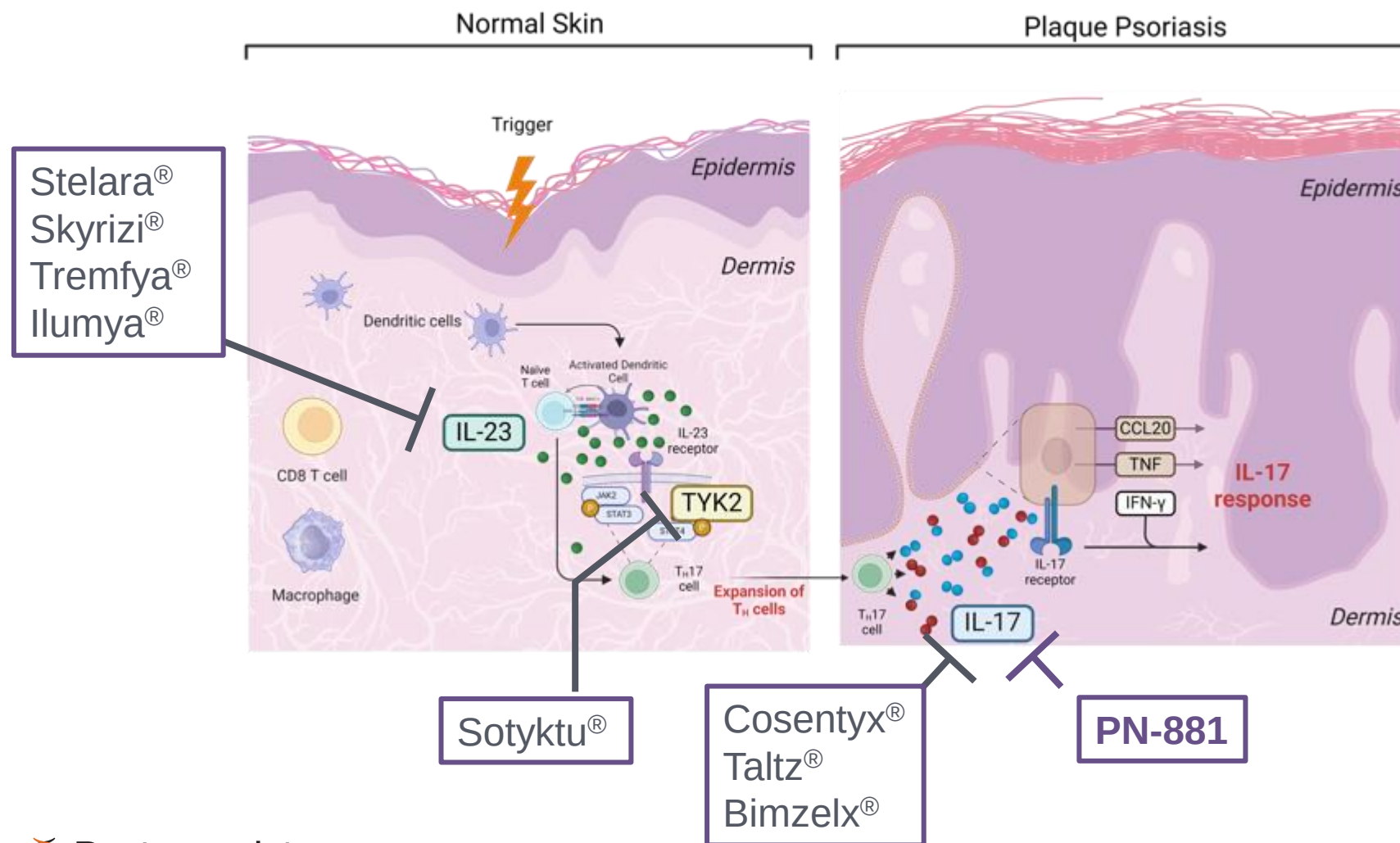
HS: Hidradenitis Suppurativa
SpA: Spondyloarthritis
PsO: Plaque Psoriasis
PsA: Psoriatic Arthritis
IBD: Inflammatory Bowel Diseases (Crohn's and Ulcerative Colitis)

Psoriasis Market Share by Drug Class

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

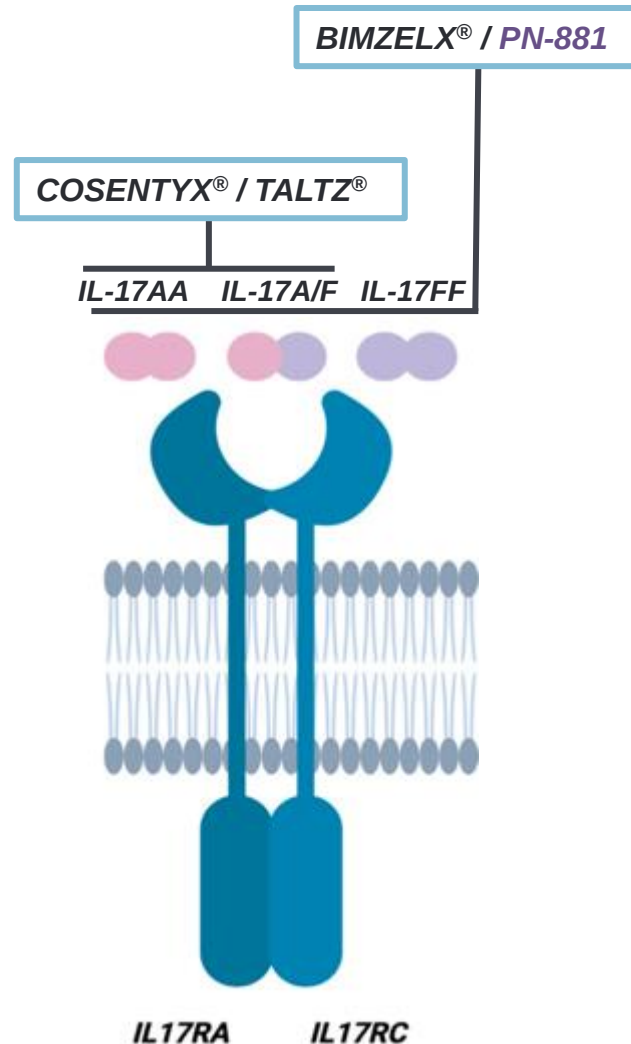


Targeting IL-17 Results in Rapid Onset of Response



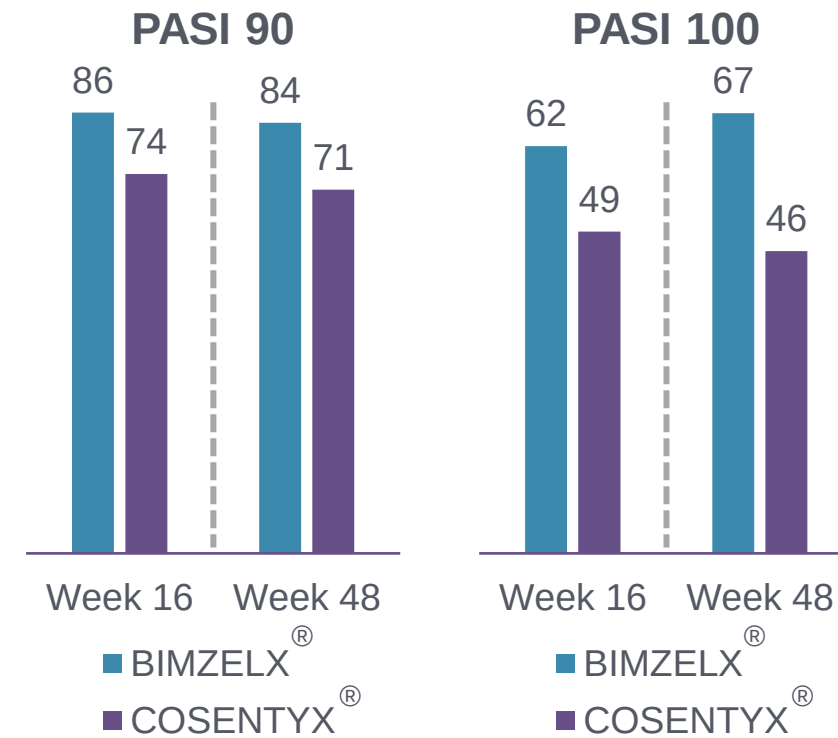
- IL-17 and IL-23 pathways are key mediators of psoriasis pathogenesis
- Proximity of IL-17 to skin pathology may lead to more rapid disease response

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 Psoriasis¹

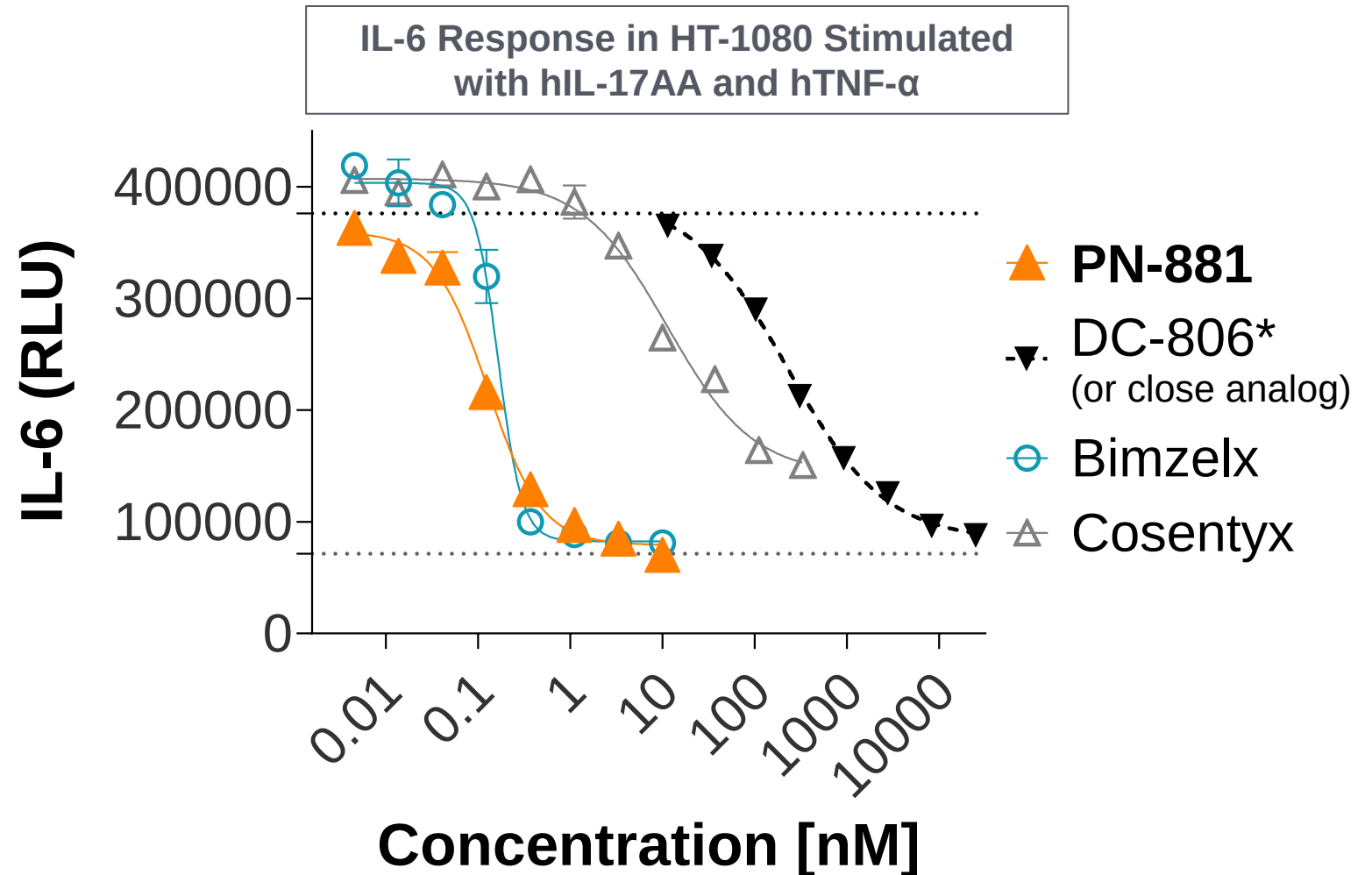
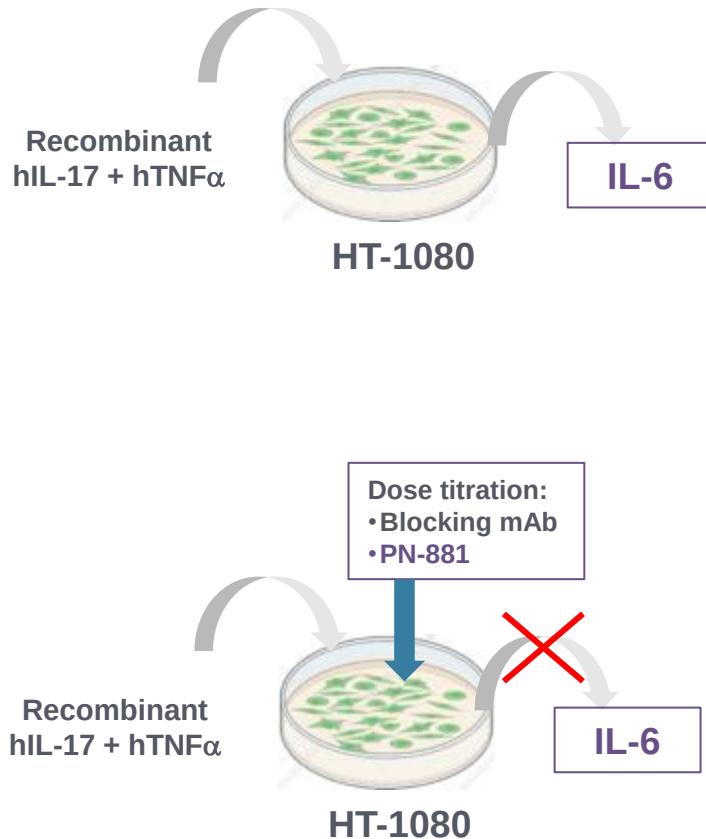


Selection of IL-17 Antagonist PN-881 as Development Candidate

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 ✓
<i>In vivo</i> Pharmacokinetics	• Mouse ✓ • Rat ✓ • Dog ✓ • Cynomolgus monkeys ✓
<i>In vivo</i> Pharmacodynamics	• Reduction in IL-17-induced CXCL1 after oral administration ✓
Tissue Distribution	• Mouse ✓ • Mini-pig ✓
Efficacy Model	• Rat IL-23-induced skin inflammation model ✓

PN-881 Potently Inhibits IL-17AA

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



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

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



Lead Peptide and Competitors	HT-1080 (nM)					
	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* (or close analogue)	228	3323	ND	ND	Inactive	Inactive
Injectable agents						
Cosentyx®	11	118	151	604	Inactive	Inactive
Taltz®	0.12	0.35	ND	ND	Inactive	Inactive
Bimzelx®	0.17	0.32	19	26	13	16

Similar results observed in human dermal neonatal fibroblasts (HDFn) after stimulation with IL-17AA, IL-17AF, or IL-17FF. ND: Not determined

PN-881 Achieves Desired Pharmacology in Preclinical Models

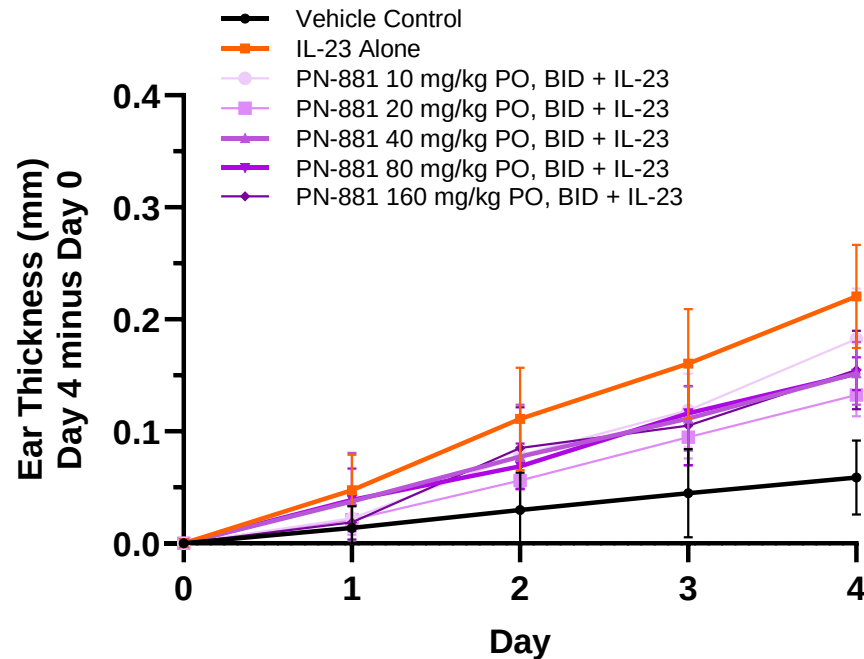


- High systemic exposures after oral administration to mice, rats, dogs, and cynomolgus monkeys
 - >100 ng/mL in cynomolgus monkeys with oral dose of 2.5 mg/kg
- Blockade of IL-17 in *in vivo* mouse models after oral administration
 - PN-881 inhibits CXCL1 production in serum and in skin in mice challenged with supra-physiologic doses of human IL-17
- Suitable tissue distribution into the skin in preclinical models
 - Ratio of skin to plasma concentrations comparable to or better than monoclonal antibodies

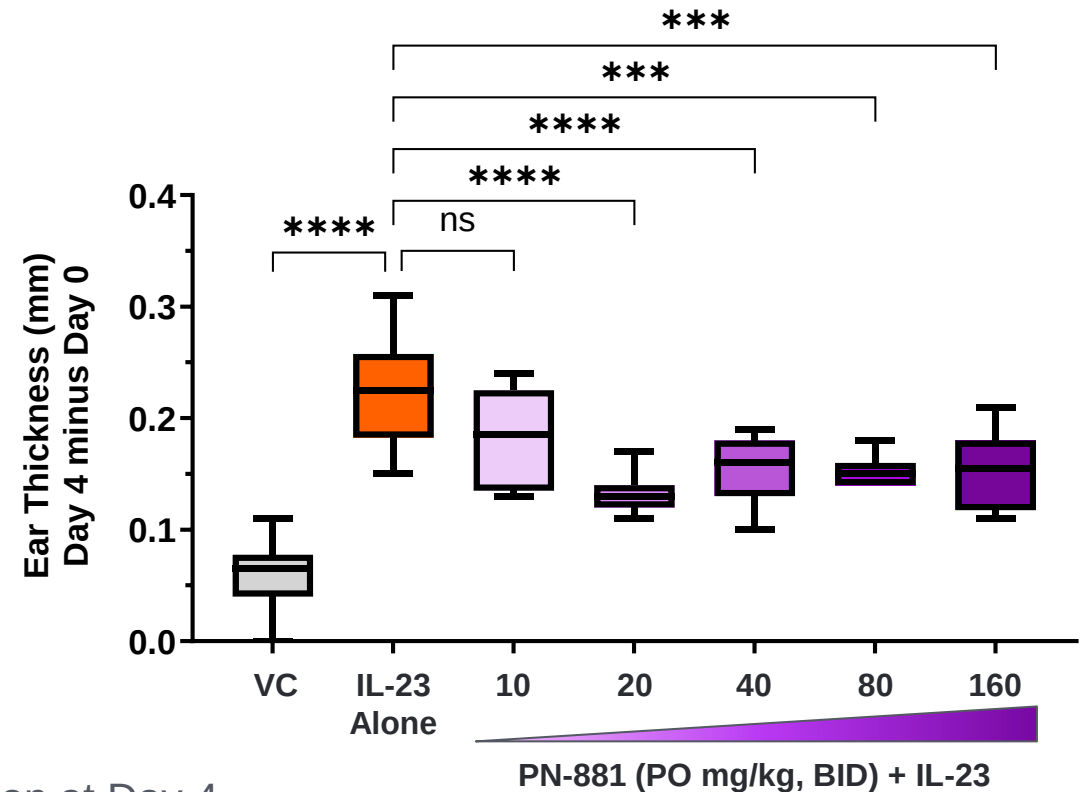
PN-881 in the Rat IL-23-induced Skin Inflammation Efficacy Model

PN-881 significantly reduces IL-23-induced ear thickness after oral administration

Ear Thickness Change Over Time



Ear Thickness Change (Day 4)



- Oral PN-881 significantly reduced IL-23-induced ear inflammation at Day 4
- IL-23-induced inflammation was significantly lower over the 4-day study with PN-881 treatment
- **Results demonstrate that PN-881 significantly reduced IL-17-mediated ear inflammation in the IL-23 challenge model**

IL-23 (1.5 µg/animal) administered daily via intradermal injections in the ear.

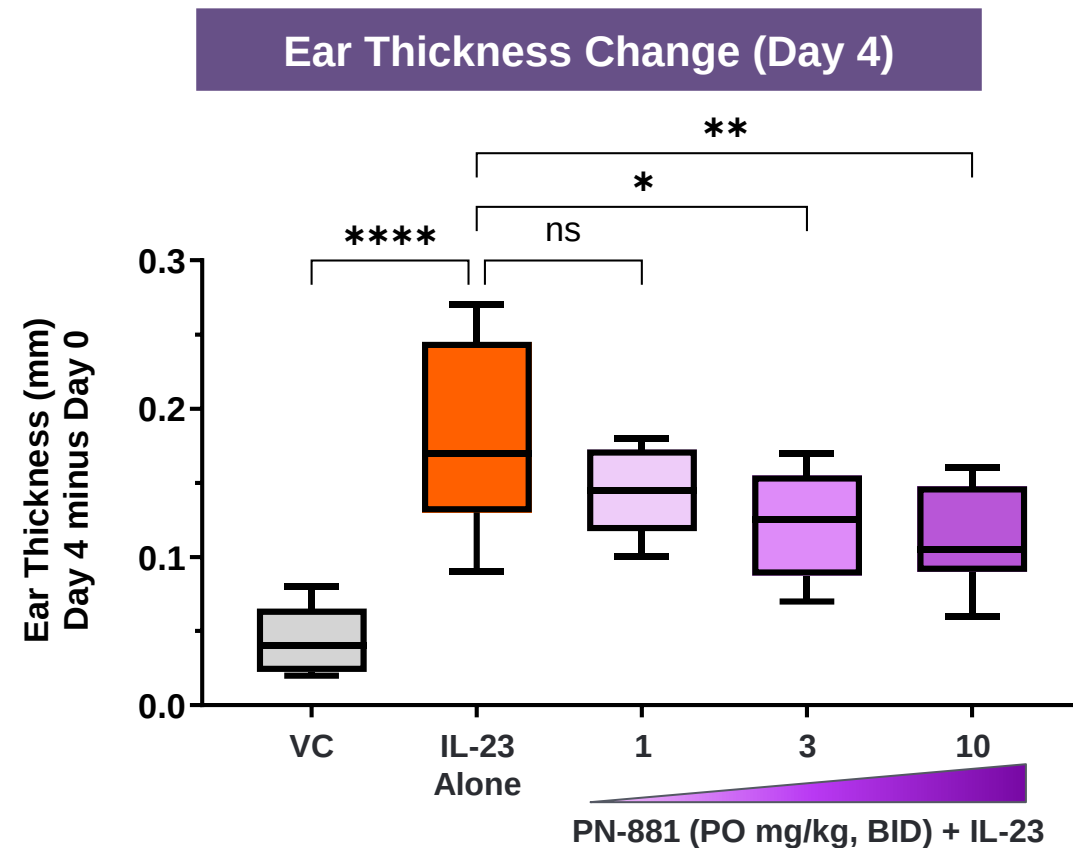
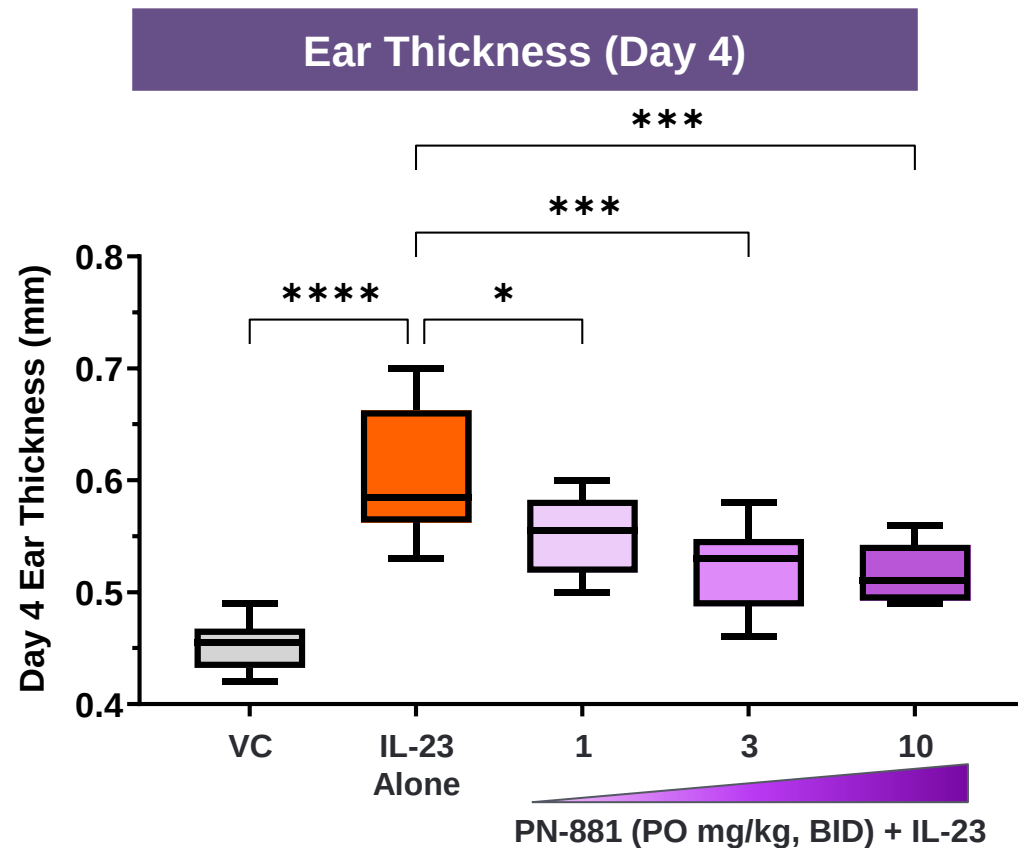
VC = vehicle control. ns = not significant. BID = twice daily. ***p < 0.001, ****p < 0.0001.

Data points depict mean ± standard deviation; boxes depict median and interquartile ranges; bars depict minima and maxima.

Data combined from two experiments (n = 8-16/group).

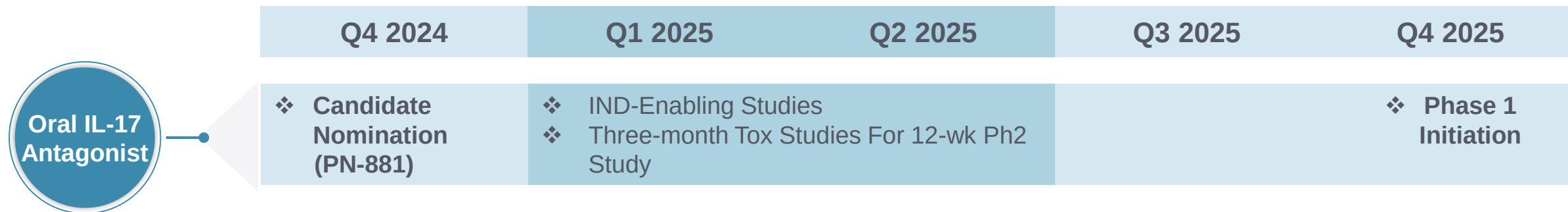
PN-881 in the Rat IL-23-induced Skin Inflammation Efficacy Model

PN-881 significantly reduces IL-23-induced ear thickness after oral administration



- Oral PN-881 significantly reduced IL-23-induced ear inflammation by Day 4 at low doses
- Results demonstrate that PN-881 significantly reduced IL-17-mediated ear inflammation in the IL-23 challenge model**

PN-881: Near-Term Clinical Development Plan



- IND-enabling studies
 - Initiated manufacturing to support toxicology and early clinical development
 - Accelerated toxicology studies to include up to 3-month Tox studies
- Planned clinical studies
 - Phase 1 single ascending dose (SAD), multiple ascending dose (MAD) trial to initiate in 2H25
 - Results of the Phase 1 SAD/MAD will inform design and dosing in a dose-ranging psoriasis trial
 - Rapid expansion into other IL-17-mediated diseases including psoriatic arthritis, hidradenitis suppurativa, and axial spondyloarthropathies gated based on results in psoriasis

Thank you

Addendum Back-up Slides

Ichotrokinra (JNJ-2113)

Preclinical Data

- **Highly potent (single digit picomolar) oral IL-23R antagonist**
 - >1000-fold more potent vs first-generation candidate PTG-200 (PBMC, phospho-STAT3 assay)
 - Similar or better target affinity vs. IL-23 mAbs
 - **High oral stability**
 - Ex-vivo stability: >24hr half-life in feces (human, cyno, and rat)
 - In-vivo stability: >25% fecal recovery after 24hrs in cynos
 - Significantly improved stability vs. PTG-200
 - **Not gut-restricted**
 - First-generation candidate PTG-200 was designed as a gut-restricted peptide
-
- **Pre-clinical Proof-of-Concept:**
 - Achieved pre-clinical PoC with oral dosing in IL-23-induced rat ear skin inflammation model
 - Similar inhibition to systemic IL-23 mAbs
 - Achieved pre-clinical PoC with oral dosing in TNBS-induced rat colitis model
 - Minimal efficacy dose significantly lower for TNBS colitis study vs. skin inflammation study

IL-23R binding affinity and potency of Icotrokinra (JNJ-2113) against IL-23–mediated responses in cells

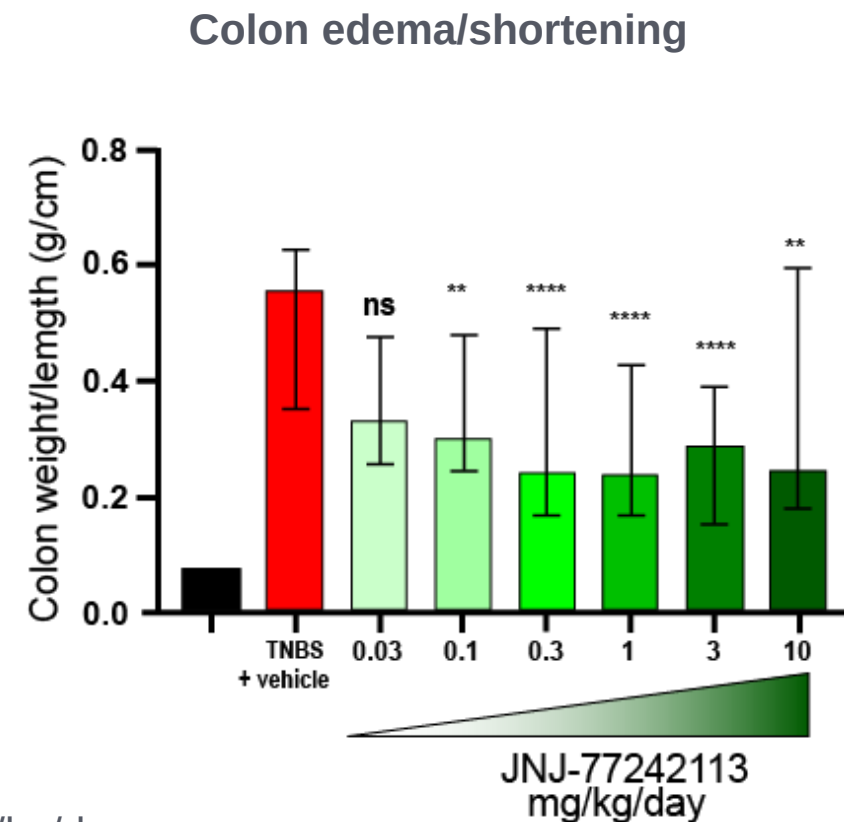
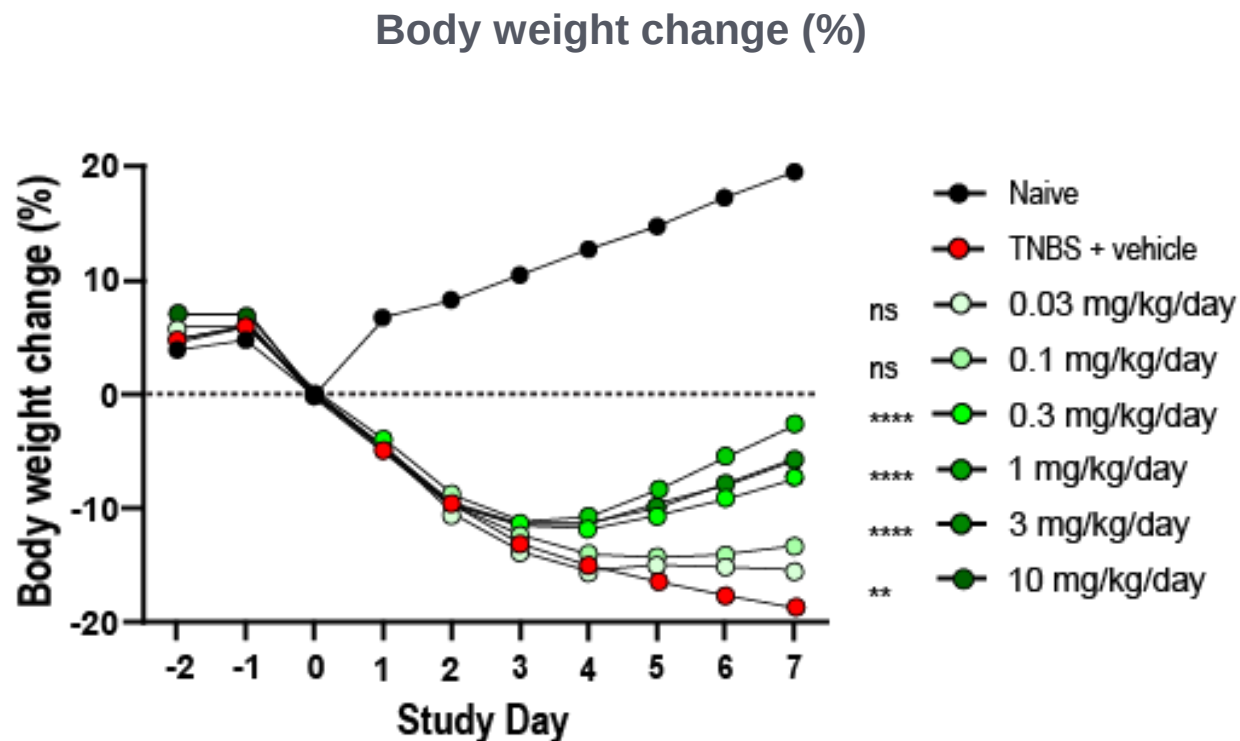
In vitro protein/cells	Binding affinity/IL-23–induced endpoint	JNJ-2113 K _D or IC ₅₀ (pM)	K _D /IC ₅₀ range ^c	n ^d
Human IL-23R ECD (SPR in vitro)	Binding affinity (K _D)	7.1 ± 2.5	4–10	5
Human PBMC	IL-23–induced STAT3 phosphorylation	5.6 ± 1.2	4.3–6.6	3
Human PBMC	IL-12–induced STAT4 phosphorylation ^a	>2,000,000	–	2
Human NK cells	IL-23–induced IFN γ production	18.4 ± 6.2	12.4–28.3	5
Human (healthy) whole blood	IL-23–induced IFN γ production	11 ^b	4–91	15
Human (psoriasis) whole blood	IL-23–induced IFN γ production	9 ^b	0.5–35	4
Rat IL-23R ECD (SPR in vitro)	Binding affinity (K _D)	17.5 ± 7.8	12–23	2
Rat whole blood	IL-23–induced IL-17A production (20 ng/mL IL-23)	250 ± 62	160–340	6
Rat whole blood	IL-23–induced IL-17A production (4 ng/mL IL-23)	54 ± 34	12–110	8

ECD extracellular domain, IC50 50% inhibitory concentration, IFN interferon, IL interleukin, K_D disassociation constant, NK natural killer, PBMC peripheral blood mononuclear cells, SPR surface plasmon resonance, STAT signal transducer and activator of transcription.

^aImpact on IL-12 signaling in same PBMCs to assess selectivity. ^bValues for human whole blood IC50s are median values; all others are mean values. ^cRange indicates minimum and maximum values obtained across independent experiments. ^dNumber of independent experiments, n.

Pre-Clinical PoC 1: Rat TNBS-Induced Colitis Model

Orally Dosed Icotrokinra (JNJ-2113) Attenuates Weight Loss and Colon Inflammation



- Statistically significant effects seen beginning at doses of 0.1 to 0.3 mg/kg/day
- Although exposure in plasma and skin was much lower than GI tissues, exquisite potency of JNJ-2113 indicated potential for systemic activity beyond the GI tract

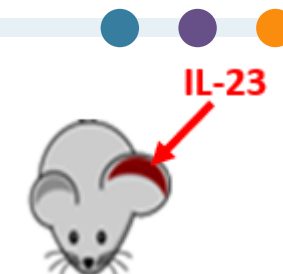
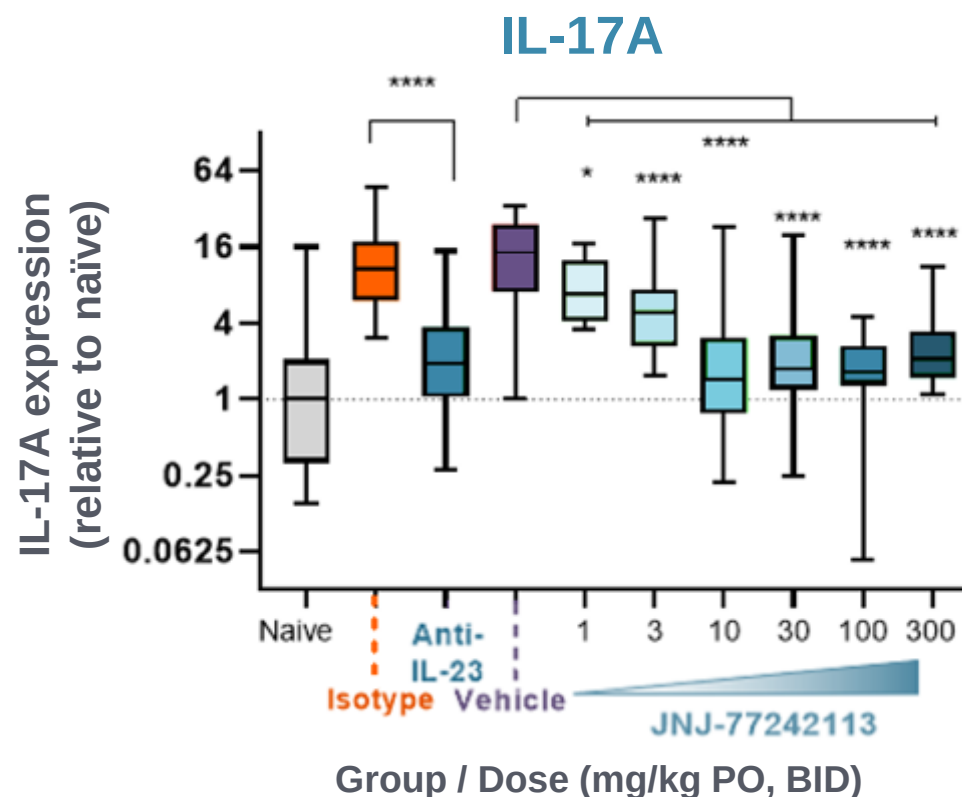
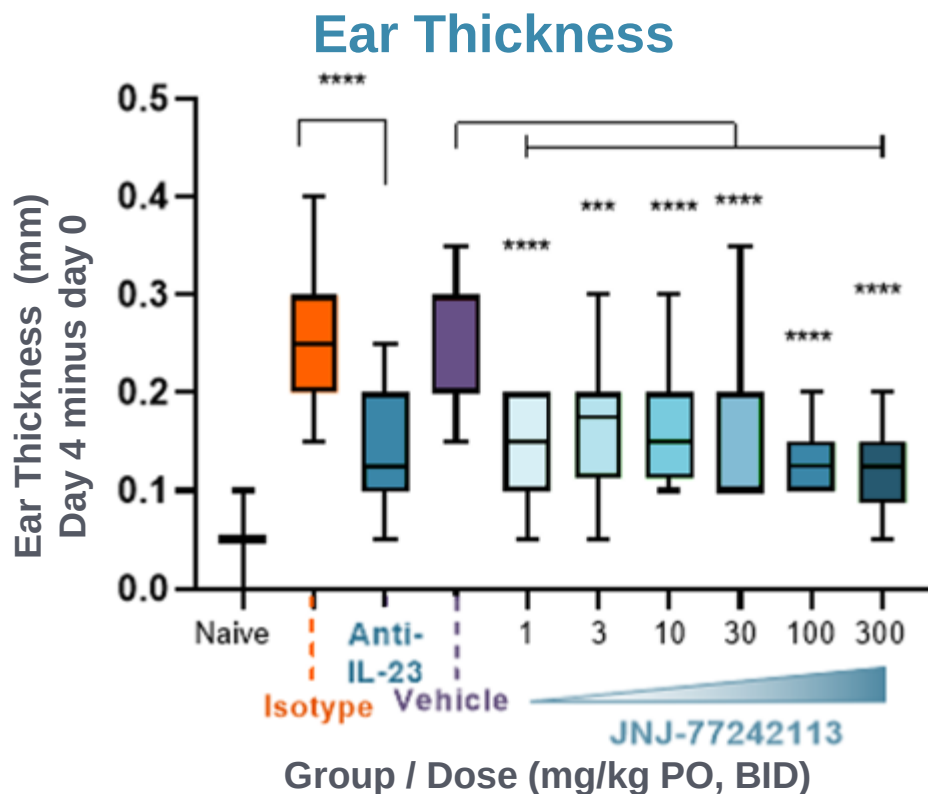
GI=Gastrointestinal; TNBS=Trinitrobenzenesulfonic acid.

ns=not significant, **p < 0.01, ****p < 0.0001. Graph on right represents median and interquartile range. Data combined from three studies.

Fourie AM, et al. *Scientific Reports*. 2024;14:17515; 1-12.

Pre-Clinical PoC 2: Rat IL-23 Induced Skin Inflammation Model

Orally Dosed Icotrokinra (JNJ-2113) Achieves Inhibition Equivalent to Anti-IL-23 Antibody



- Doses ≥ 1 mg/kg BID reduced inflammation and cytokine induction (IL-17A, IL-17F and IL-22)
- Doses ≥ 10 mg/kg BID showed equivalent inhibition to an anti-IL-23 antibody

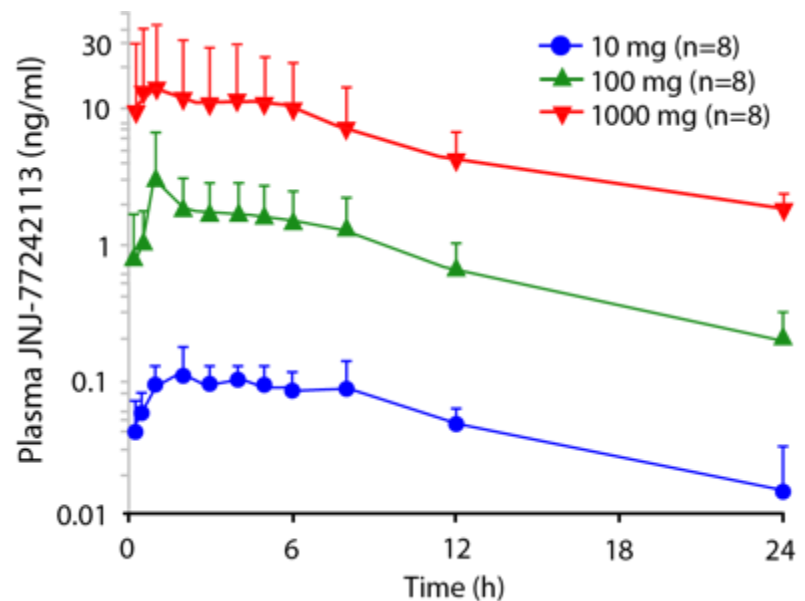
BID=Twice daily. Anti-IL-23 and isotype control dosed intraperitoneally on days -1 and 3.

ns=not significant, * $p < 0.05$, *** $p < 0.001$, **** $p < 0.0001$. Boxes depict median and interquartile ranges; bars depict minima and maxima. Data combined from three experiments.

Phase 1 Study of JNJ-2113 in Healthy Volunteers

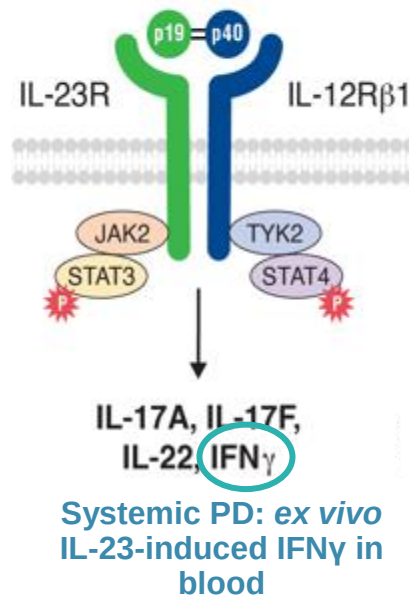
Safety, Pharmacokinetics, Systemic Pharmacodynamics

Human PK Profile[†] Supports Pathway Coverage

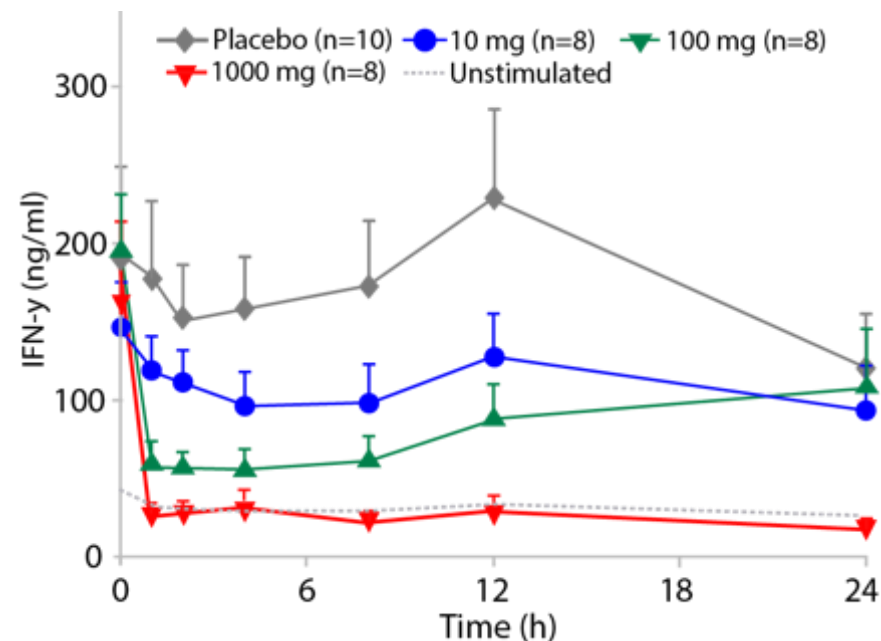


Mean plasma concentrations of JNJ-2113 in healthy participants from Part 2 (Day 1 in multiple ascending dose cohorts)

IL-23



Robust Systemic PD Activity with Oral Dosing



Mean concentrations of IL-23-induced IFN γ in whole blood from participants after receiving a single oral dose of JNJ-2113

- Demonstrated PoC for systemic PD activity of orally dosed JNJ-2113 in humans
- Single and multiple oral doses were safe and generally well tolerated with no safety signal of concern

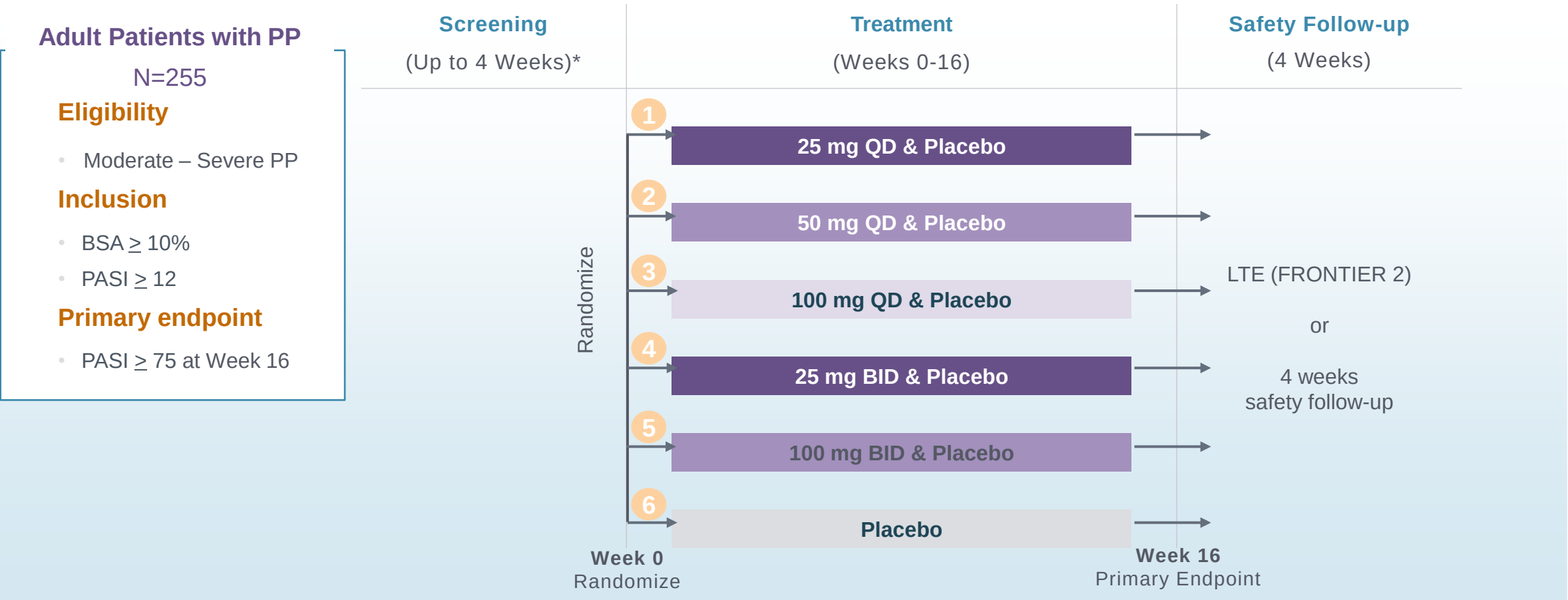
PD=Pharmacodynamic; PK=Pharmacokinetic; PoC=Proof of Concept.

PK data represent mean + SD.

[†]Phase 1 conducted under fasted conditions.

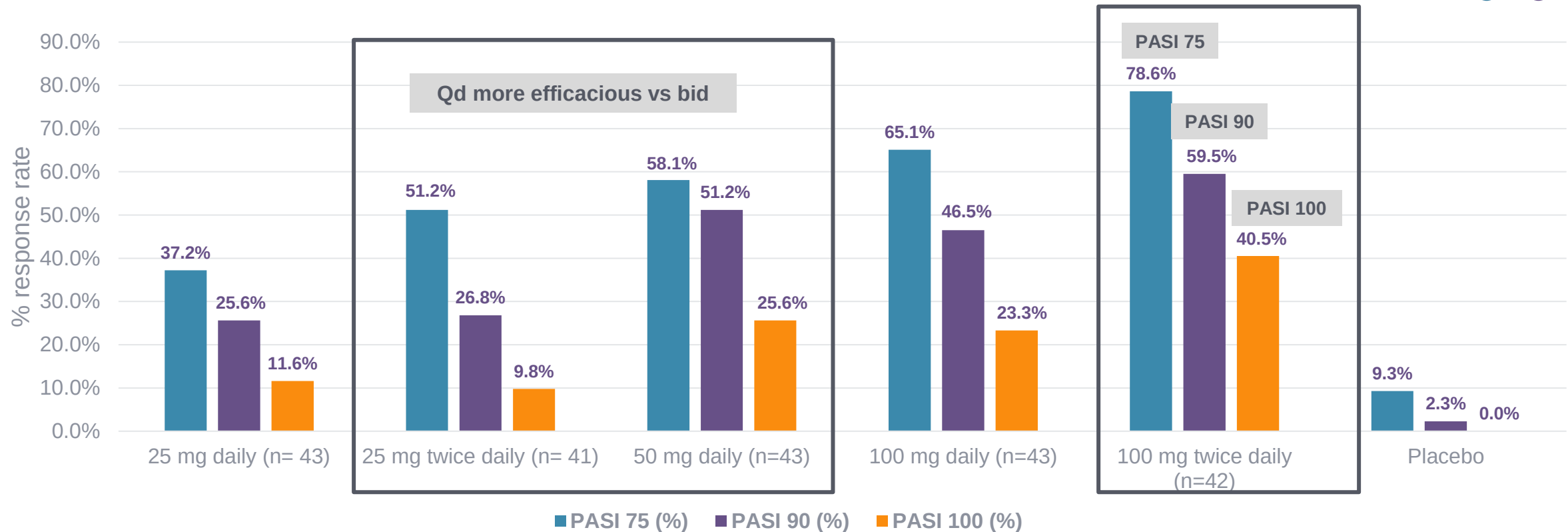
JNJ-2113 FRONTIER 1 Phase 2b Plaque Psoriasis (PsO) Study

A Phase 2b multicenter, randomized, placebo controlled, dose-ranging study to evaluate the efficacy and safety of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis



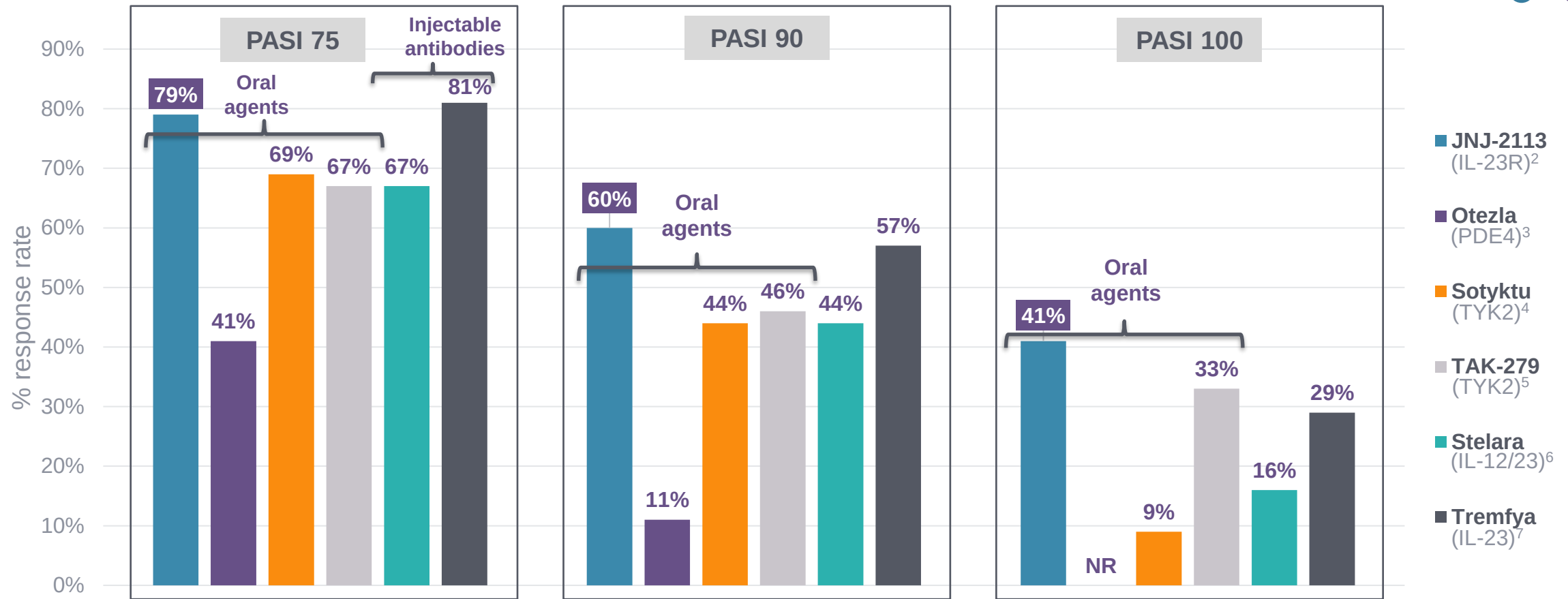
Icotrokinra (JNJ-2113) Phase 2B Frontier 1 16-Week Data

Dose Response



- 200 mg once daily oral dose selected for all five phase 3 psoriasis studies
- PASI 90 as a high-bar primary endpoint in these phase 3 studies

Cross-Study Comparison of Icotrokinra (JNJ-2113) to Clinically Relevant Phase 2 Benchmarks¹



1. Cross trial (not head-to-head) comparisons
2. JNJ-2113 100 mg bid dose. Wk 16 endpoint (Placebo: PASI 75: 9.3%, PASI 90: 2.3%, PASI 100: 0%)
3. Otezla 30 mg qd approved dose. Week 16 primary endpoint. Papp K et al. Lancet 2012; 380: 738–46. (Placebo: PASI 75: 5.7%, PASI 90: 1.1%, PASI 100: NR)
4. Sotyktu 3 mg bid dose (6 mg qd dose approved). Wk 12 primary endpoint. Papp K et al. N Engl J Med 2018; 379:1313-1321. (Placebo: PASI 75: 7%, PASI 90: 2%, PASI 100: 0%)
5. TAK-279 30 mg qd dose (Expected phase 3 dose). Wk 12 primary endpoint. AAD 2023. (Placebo: PASI 75: 5.8%, PASI 90: 0%, PASI 100: 0%)
6. Stelara 45 mg wklly x 4 (~approved 90 mg week 0 and 2 approved dose). Wk 12 primary endpoint. Krueger et al. N Engl J Med 2007;356:580-92. (Placebo: PASI 75: 2%, PASI 90: 2%, PASI 100: 0%)
7. Tremfya 200 mg wk 0, 4, then q 8 wks (approved dose 100 mg wk 0, 4 then q 8 wks). Wk 16 primary endpoint. Gordon KB et al. N Engl J Med 2015;373:136-44. (Placebo: PASI 75: 5%, PASI 90: 2%, PASI 100: 0%)

Icotrokinra (JNJ-2113) FRONTIER 1 Phase 2b Plaque Psoriasis (PsO) Study

Safety Summary



The proportion of patients experiencing 1 or more AEs was comparable between JNJ-77242113 groups and the placebo group

- Most frequently reported AEs were COVID-19 and nasopharyngitis
- There was no evidence of dose-dependent increase in the occurrence of AEs across the JNJ-77242113 treatment groups



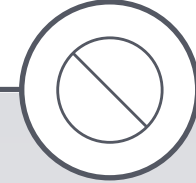
There were three serious AEs that occurred in FRONTIER-1 (n=1 each: suicide attempt, COVID-19, infected cyst; all on active drug and assessed as not related to study intervention by investigators).

No dose-dependent relationship was observed.



A low number of laboratory abnormalities occurred during the study and were comparable between placebo and JNJ-77242113 groups.

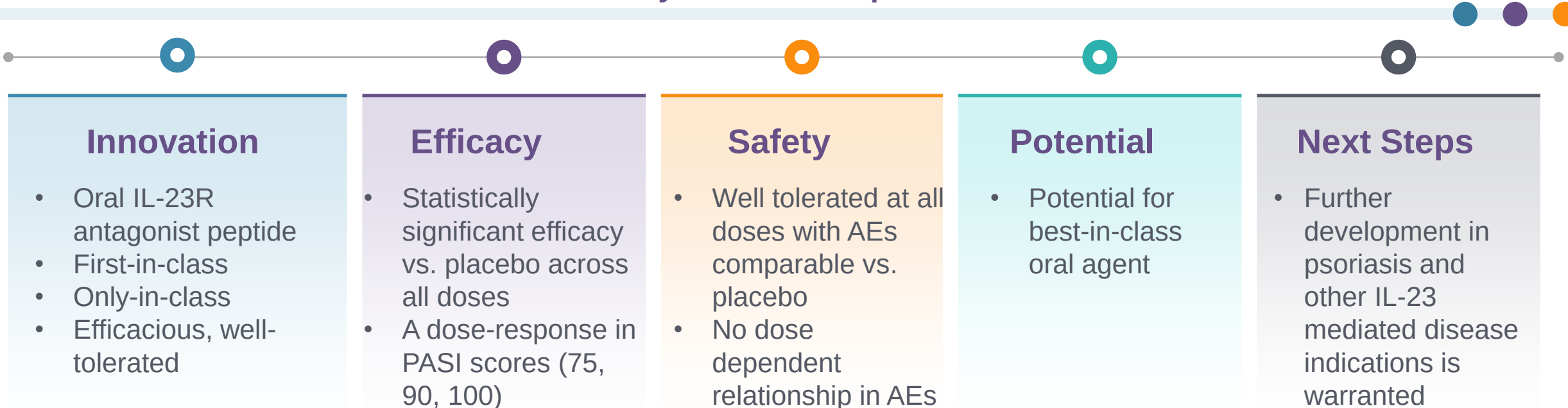
There was no evidence of a dose-dependent increase in the occurrence of abnormalities.



There were no deaths, MACE, or malignancies during the study.

Icotrokinra (JNJ-2113; formerly PN-235)

Conclusions from Phase 2b Psoriasis Study and Next Steps



Next Steps

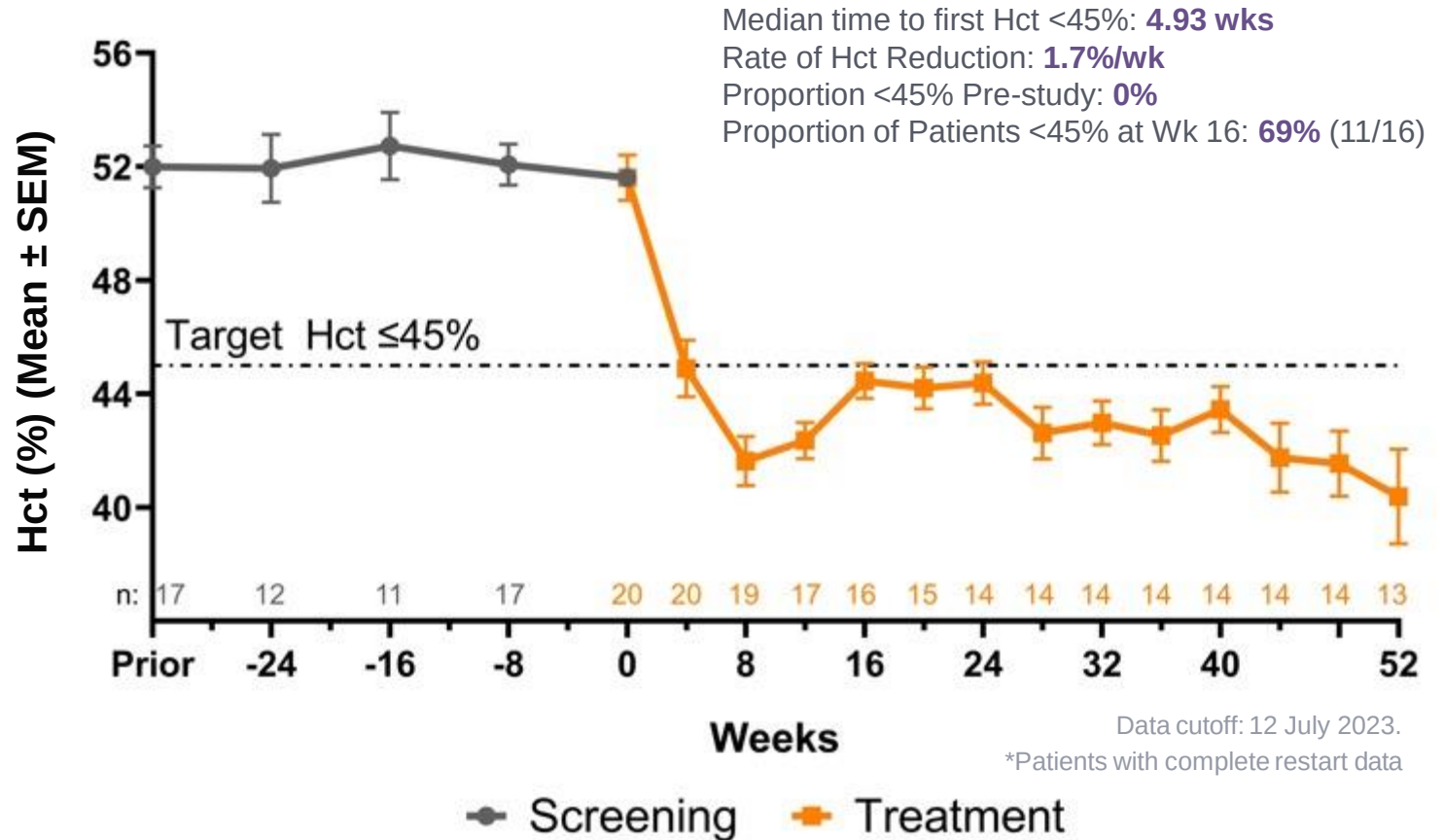
- Registrational program (ICONIC) with five phase 3 studies in psoriasis
 - Two head-to-head trials with deucravacitinib
- PASI 90 highlighted as a high-bar primary endpoint
- **200 mg oral once-daily dosing in all five phase 3 studies**

JNJ-2113 is a potential best, first-, and only-in-class oral IL-23 receptor antagonist

Clinical Study of Rusfertide in PV Patients with High Hematocrit (>48%)^{1,2}

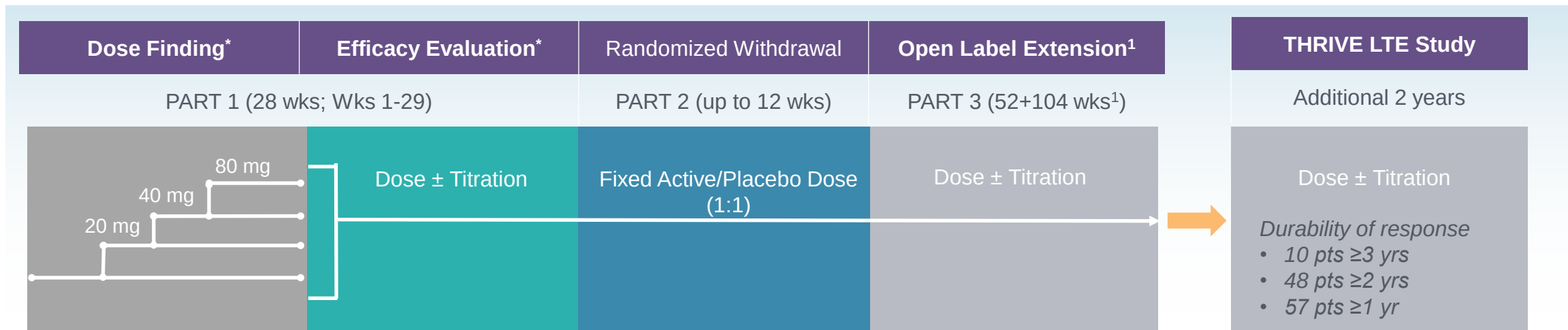
Rapid Hematocrit Control <45% Was Achieved

- Open-label, 1 year study in PV patients who are newly diagnosed or for whom current treatment is not sufficient to control hematocrit (Hct)
- Patients met WHO criteria for PV diagnosis
 - Baseline Hct >48%
 - History of ≥ 3 Hct values >48% in prior 28 wks or ≥ 5 Hct values in prior year
 - Phlebotomy alone or with concurrent cytoreductive therapy
 - Initiated rusfertide treatment without prestudy phlebotomy
- Clinical endpoints
 - Proportion of subjects with Hct <45% at week 16
 - Time to first Hct <45%
 - Safety



Phase 2 **REVIVE** Study and OLE **THRIVE** Study of Rusfertide in PV

Randomized Withdrawal **REVIVE** Study Design



*Titrate every 4 weeks to maintain hematocrit < 45%

Up to 5.8 Years of Rusfertide Therapy

REVIVE STUDY HIGHLIGHTS^{1,2}:

- In most patients, **rusfertide provided long-term durable control of hematocrit and freedom from phlebotomy** when added to standard of care therapy for PV
- Ferritin levels improved and normalized over time without evidence of iron overload
- **Rusfertide was well-tolerated**; the most common adverse events were Grade 1 or 2 injection site reactions, fatigue, pruritus, COVID-19, arthralgia, dizziness, headache, nausea, and anemia
- **47 of 58 patients (81%)** who began Part 3 **remain on rusfertide therapy^a**
- All remaining **REVIVE** patients (n = 46) have now moved into the **THRIVE** LTE study

Video Journal of Hematology and Hematological Oncology (**VJHemOnc**):

- **VJHemOnc** created a short video of **Dr. Kristen Pettit** (U. of Michigan) giving a high-level summary of the **REVIVE long-term data** she presented at **EHA'24** (13-16 June; Madrid, Spain)
- Link to video available [here](#)

Characteristics (n = 70)

AGE

Range	27-77 years (Median, 58)
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GENDER

Females	21 (30.0%)
Males	49 (70.0%)

RISK

Low	30 (42.9%)
High	40 (57.1%) [Age based – 37.1%, Thrombotic events – 20.0%]

DURATION SINCE PV DIAGNOSIS

≤1 yr	14 (20.0%)
1 - ≤3 yrs	23 (32.9%)
3 - ≤5 yrs	11 (15.7%)
>5 yrs	22 (31.4%)

CONCURRENT THERAPIES

PHL only	37 (52.9%)
PHL + HU	18 (25.7%)
PHL + IFN	8 (11.4%)
PHL + JAK inhibitor	5 (7.1%)
PHL + Multiple Agents	2 (2.9%)

NUMBER OF PHL IN 28 WEEKS PRIOR

2	1 (1.4%)
3	13 (18.6%)
4	26 (37.1%)
≥5	30 (42.9%)
Median	4 (2.9)

WEEKS BETWEEN PHLEBOTOMIES IN 28 WEEKS PRIOR

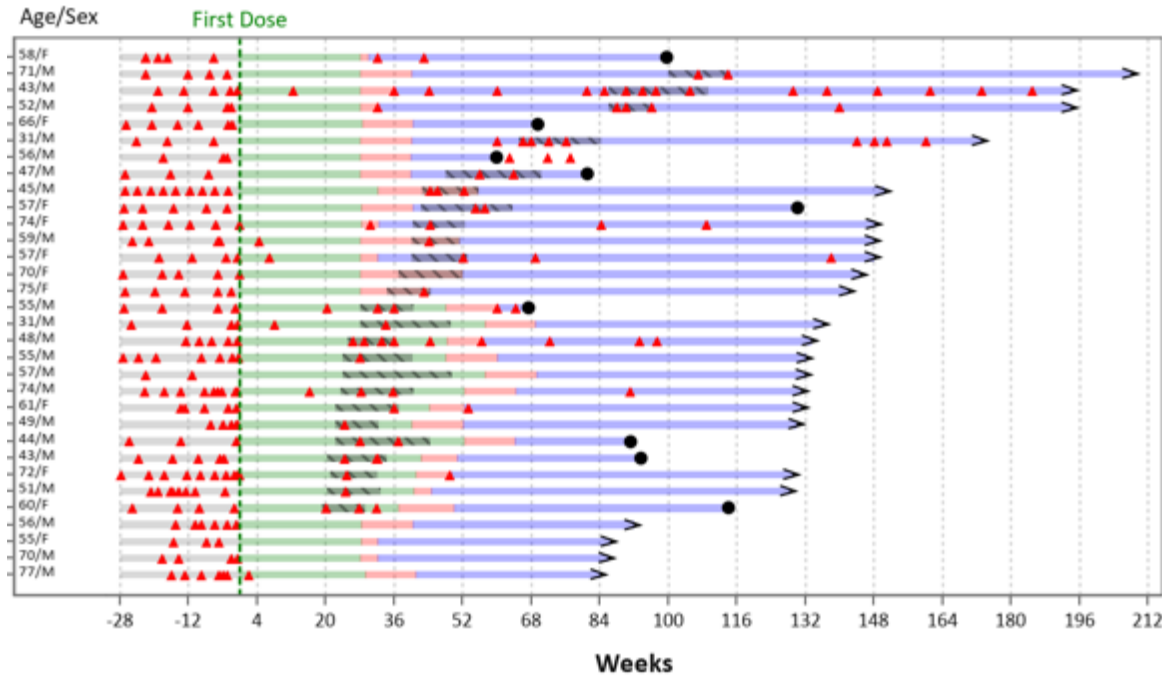
Median	5.5
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REVIVE: Durability of Rusfertide Efficacy

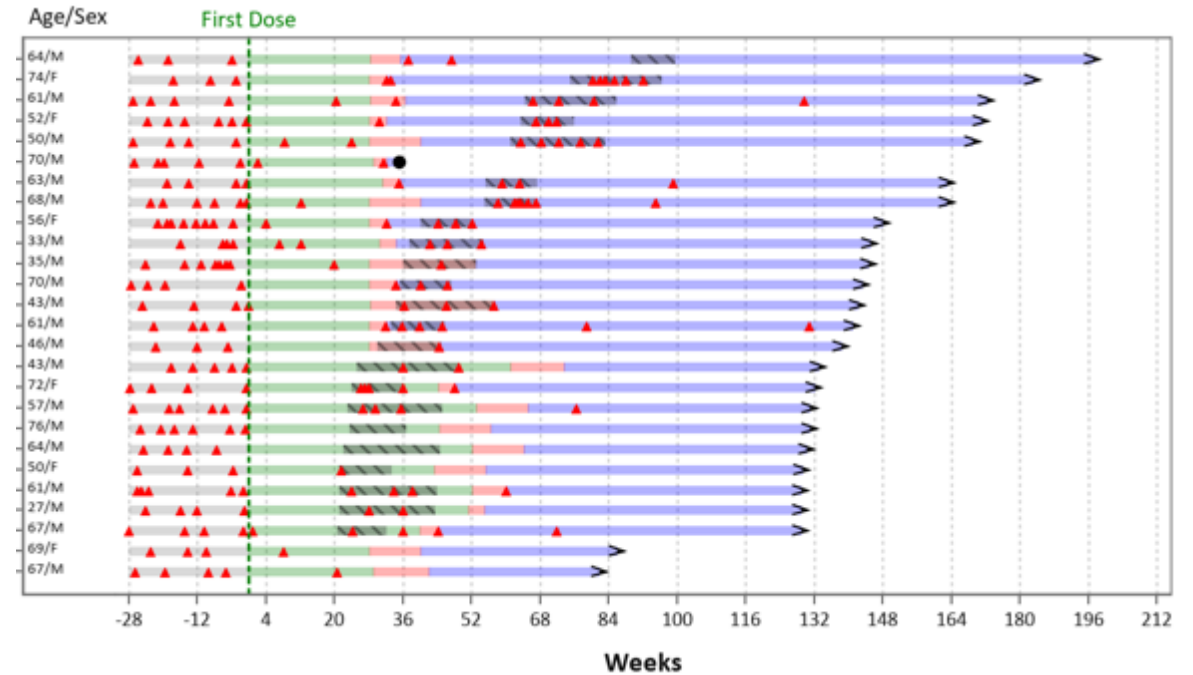
Significant Reduction in Therapeutic Phlebotomy

- In patients who continued onto Part 3, 32 (55.2%) and 26 (44.8%) patients were treated with phlebotomy alone or phlebotomy with cytoreductive therapy, respectively

Phlebotomy Only (n=32)



Phlebotomy + Cytoreductive Therapy (n=26)



Data cutoff: 17 October 2023

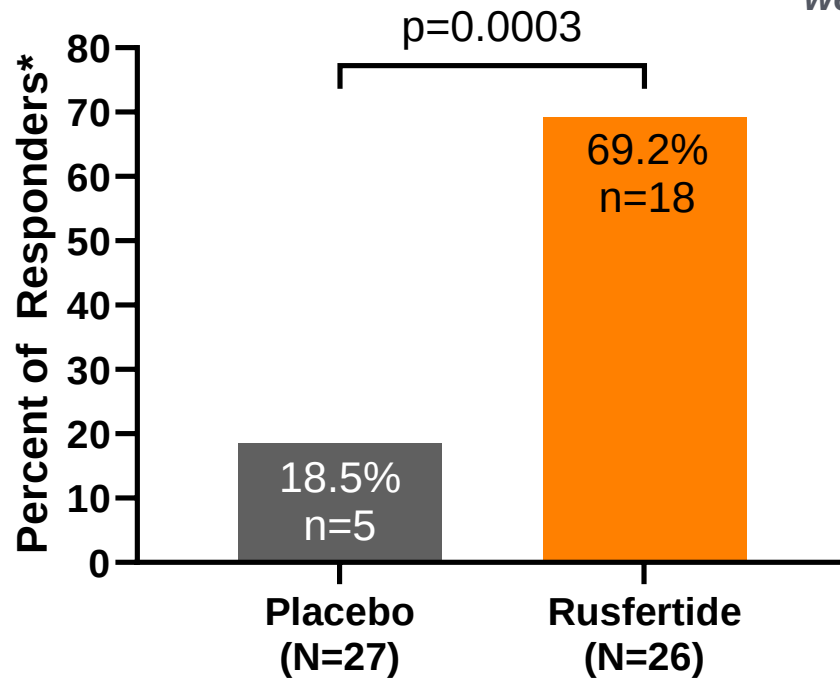
Part 2: Blinded Randomized Withdrawal Period, Weeks 29-41

Rusfertide Met Primary Efficacy Endpoint in Prespecified Full Analysis and Randomized Populations

Full Analysis Population¹

Highly Significant Efficacy in Rusfertide Arm vs. Placebo in Prespecified Primary Efficacy Endpoint

**Patient defined as a responder if they had hematocrit control, did not undergo phlebotomy, and completed the 12-week trial regimen during Part 2*

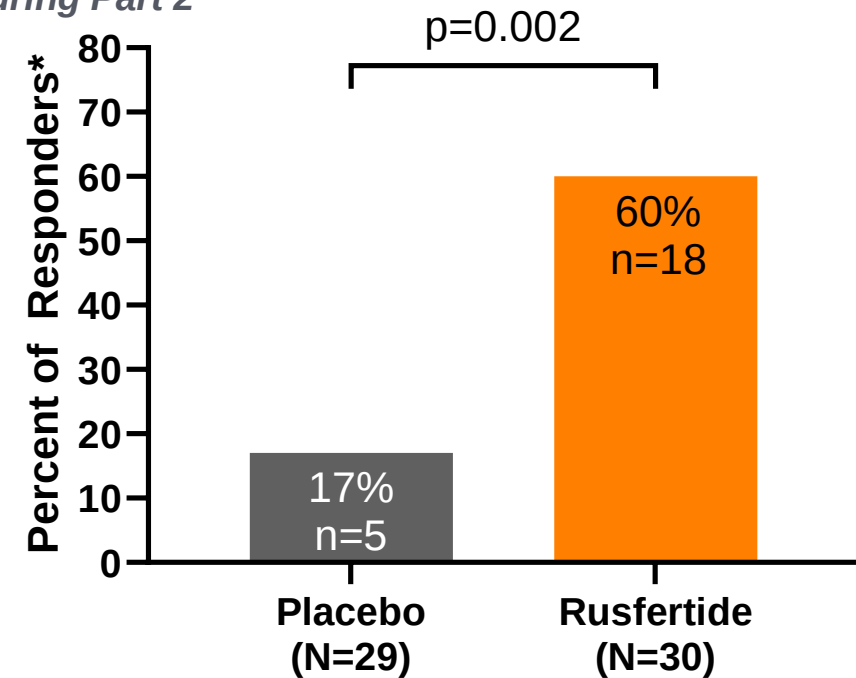


- **69.2% of patients** (18 out of 26) responded to rusfertide

– Full analysis population excludes 6 patients (4 in the rusfertide arm; 2 in the placebo arm) who discontinued early and did not complete Part 2

Randomized Population²

Highly Significant Efficacy in Rusfertide Arm vs. Placebo in Sensitivity Analysis



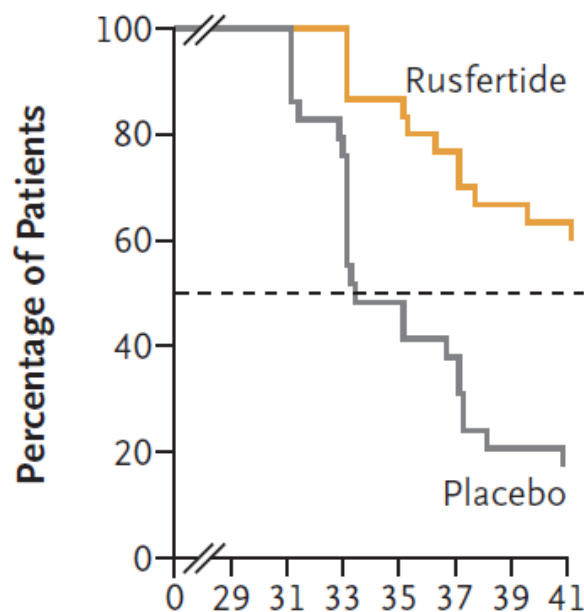
- **60% of patients** (18 out of 30) responded to rusfertide

– Randomized population includes 6 patients (4 in the rusfertide arm; 2 in the placebo arm) who discontinued early and did not complete Part 2

Phase 2 REVIVE Study: Time to Event Analysis in Randomized Population

Rusfertide Associated With Delayed Time to Loss of Response, Phlebotomy Eligibility, and First Hct $\geq 45\%$

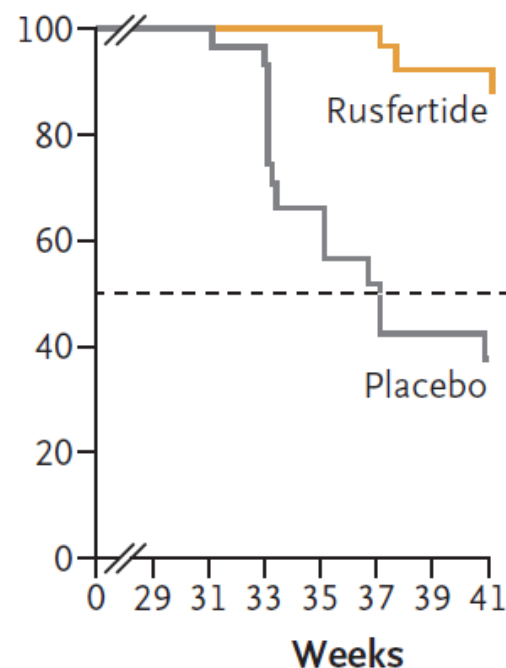
Time to Loss of Response



No. of Patients

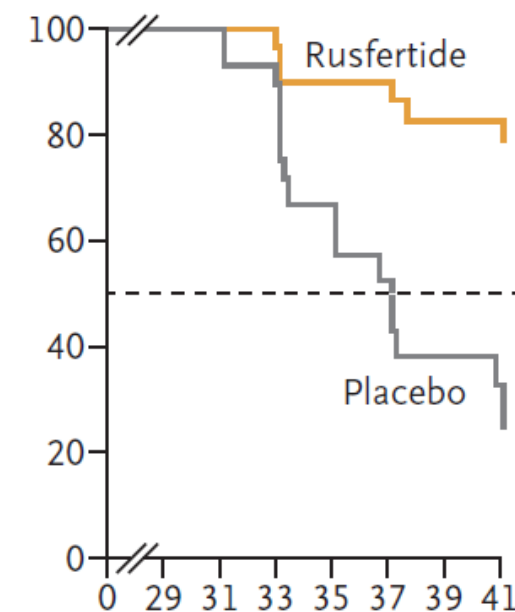
Rusfertide	30	30	26	25	21	20	15
Placebo	29	25	22	12	9	6	5

Time to Phlebotomy Eligibility



Rusfertide	30	30	30	30	22	20	15
Placebo	29	28	25	12	9	9	5

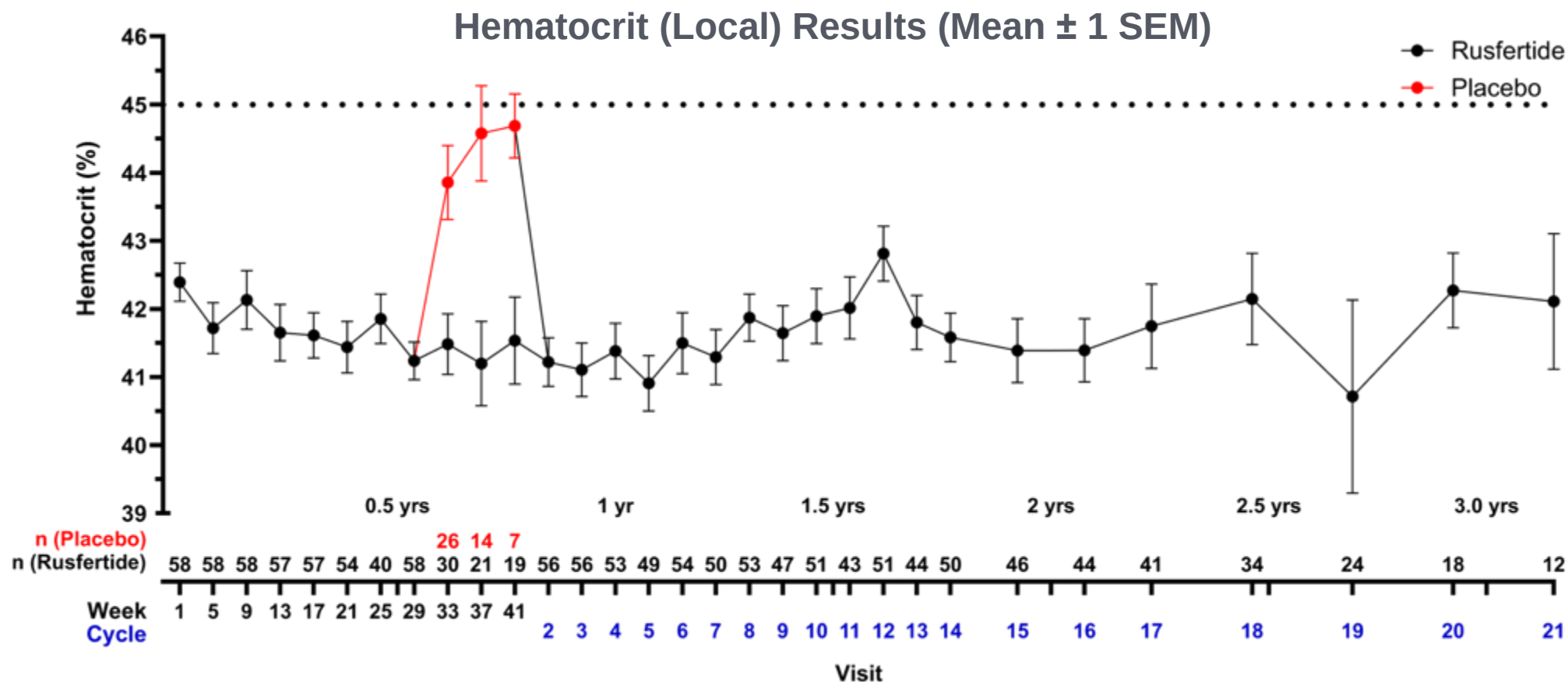
Time to First Hct $\geq 45\%$



Rusfertide	30	30	29	27	22	20	15
Placebo	29	27	25	12	9	7	3

Rusfertide Provided Durable Control of Hematocrit Through 3 Years

REVIVE Parts 1-3

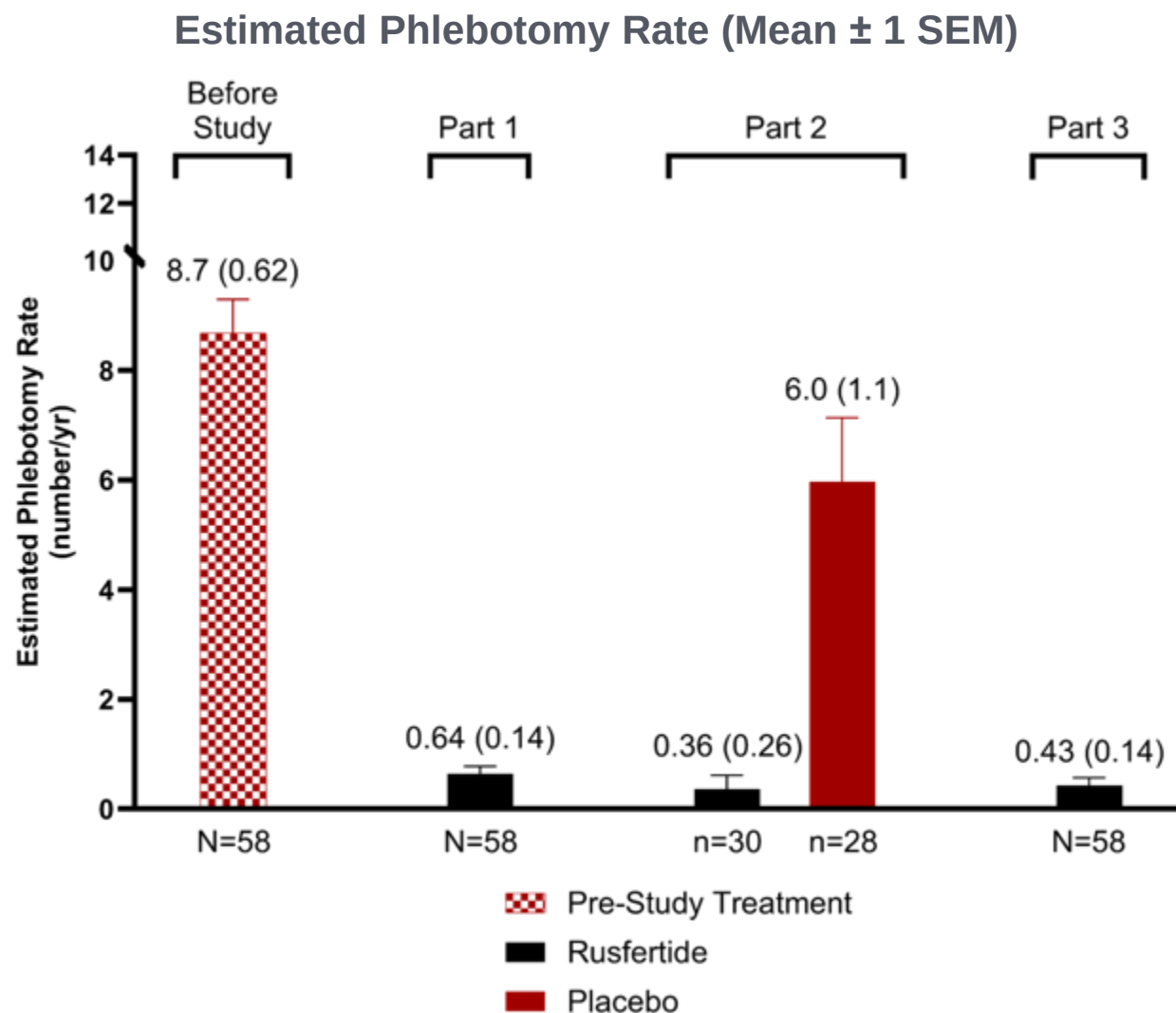


- Starting within 4 weeks of treatment initiation, rusfertide consistently maintained Hct <45%, including in patients who were on therapy for 3+ years

Data cutoff: 9 April 2024

Rusfertide Reduced the Estimated Average Phlebotomy Rate

REVIVE Parts 1-3

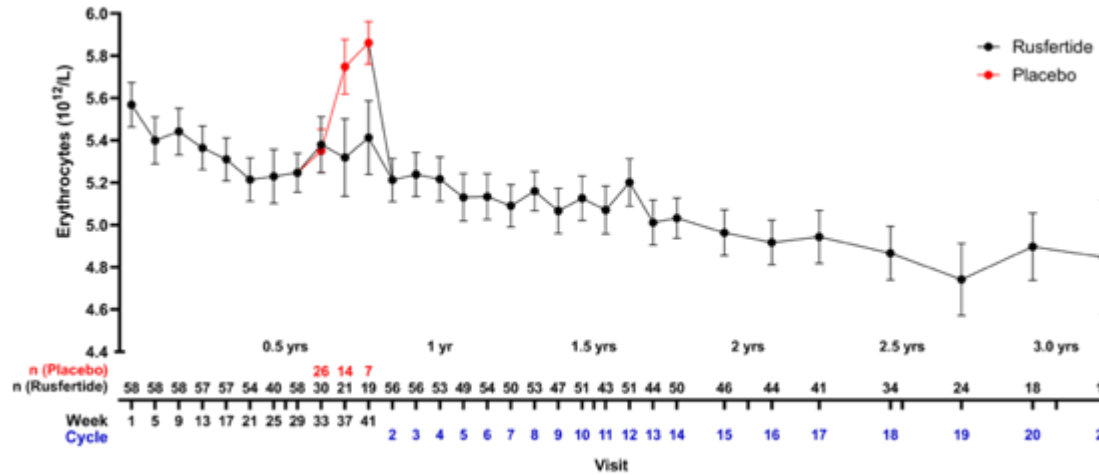


SEM, standard error of the mean; yr, year.
Data cutoff: 9 April 2024

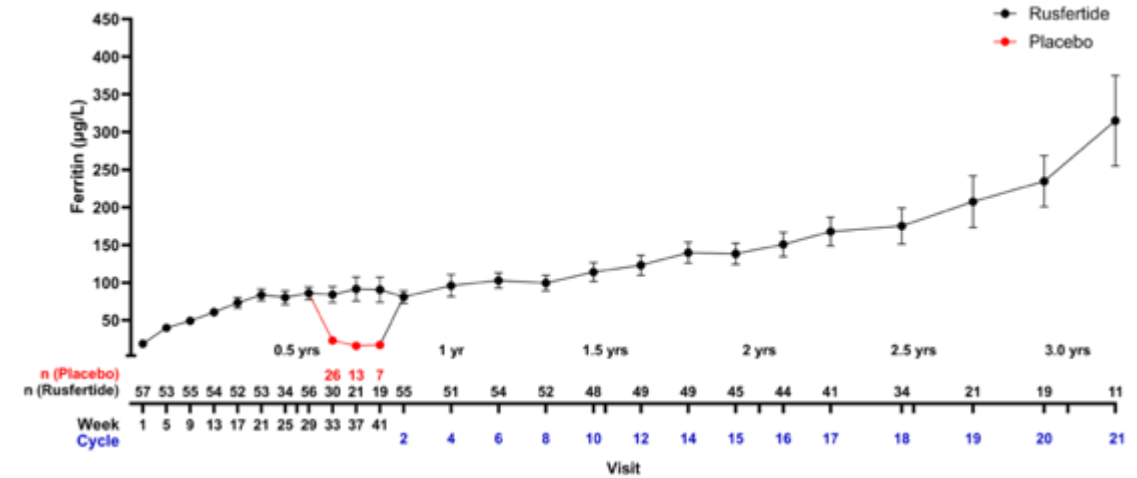
Erythrocytes Decreased Over Time; Serum Ferritin Increased Over Time

REVIVE Parts 1-3

Erythrocyte (Local) Results (Mean $\pm$ 1 SEM)



Serum Ferritin (Central) Data (Mean $\pm$ 1 SEM)



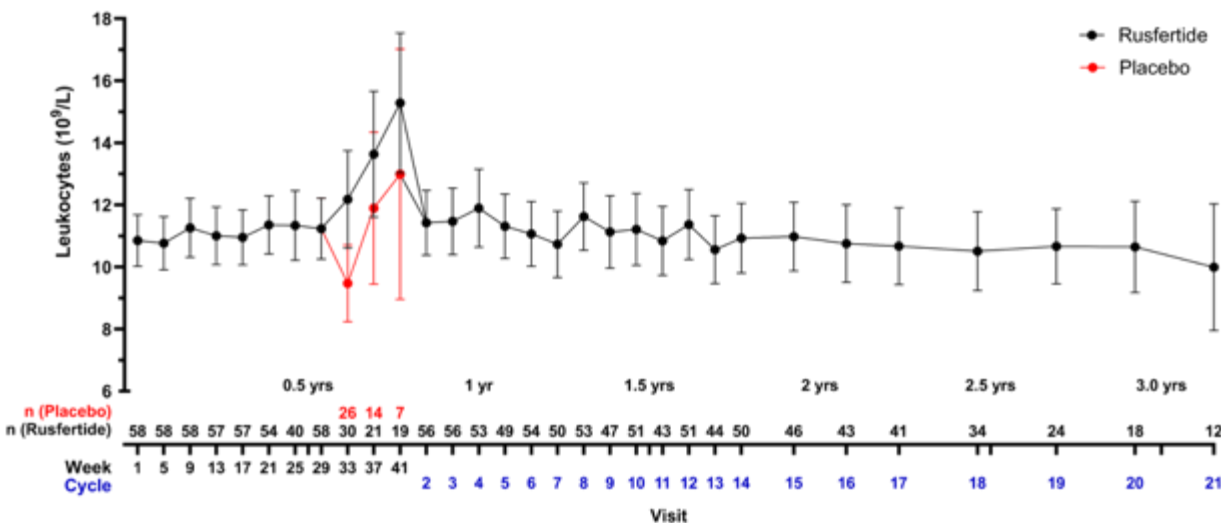
- Prior to enrollment, both erythrocytes and iron-related parameters were consistent with PV patients with systemic iron deficiency
- Erythrocyte counts decreased and stabilized over time
- Rusfertide increased serum ferritin levels over time to normal values

Leukocytes and Platelet Values Stabilized Over Time

REVIVE Parts 1-3

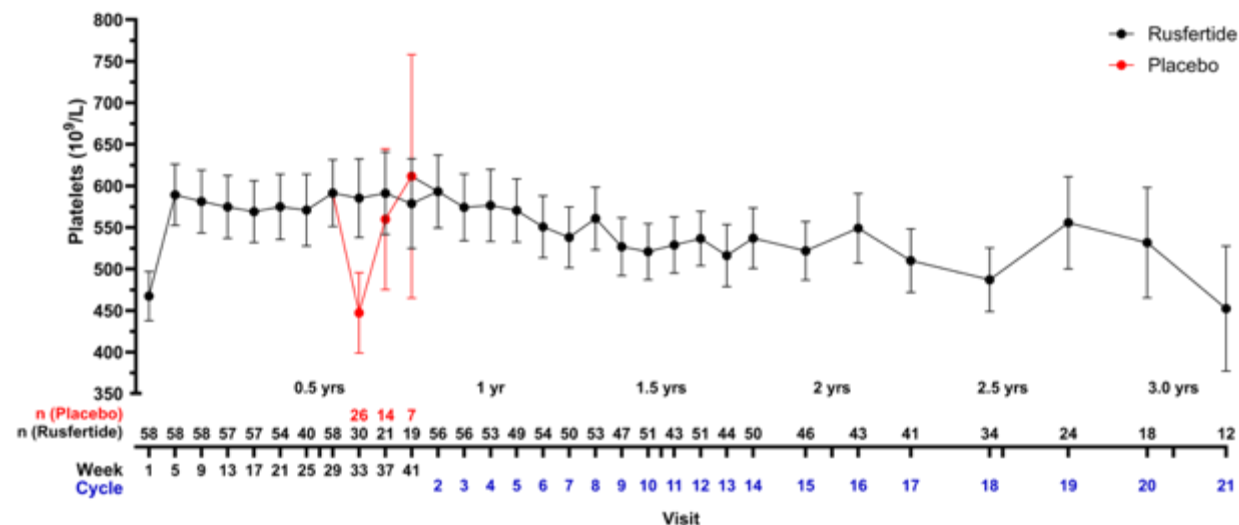


Leukocyte (Local) Results (Mean $\pm$ 1 SEM)



- Mean leukocyte counts remained stable throughout the study

Platelet (Local) Results (Mean $\pm$ 1 SEM)



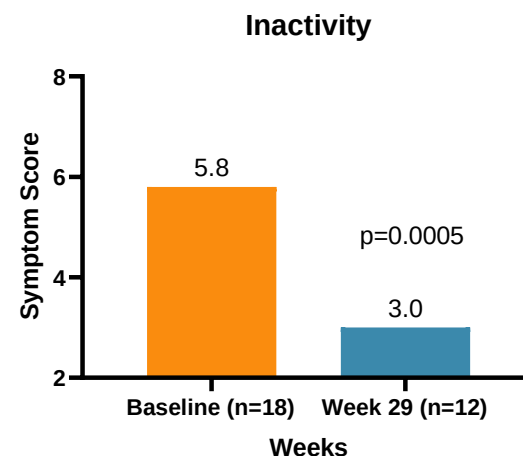
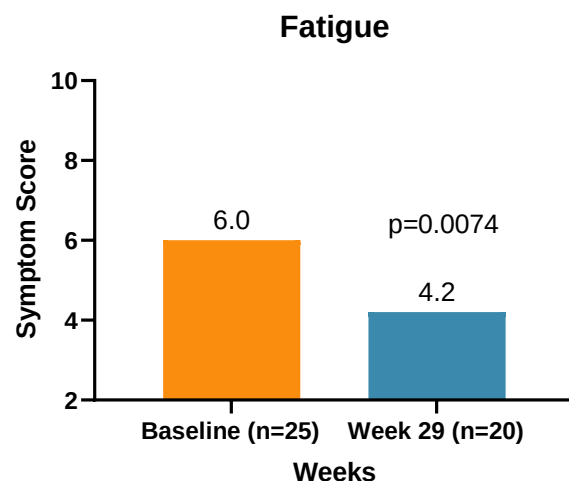
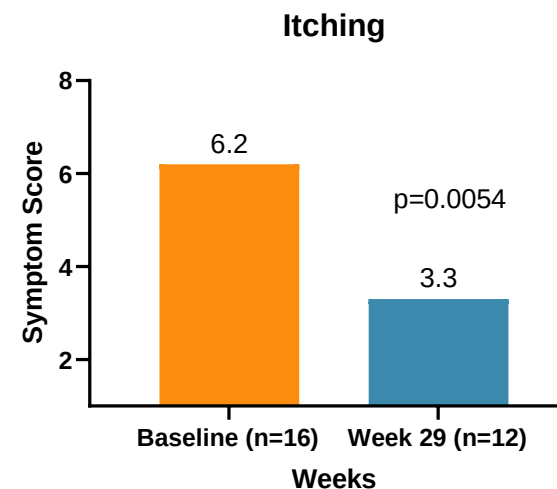
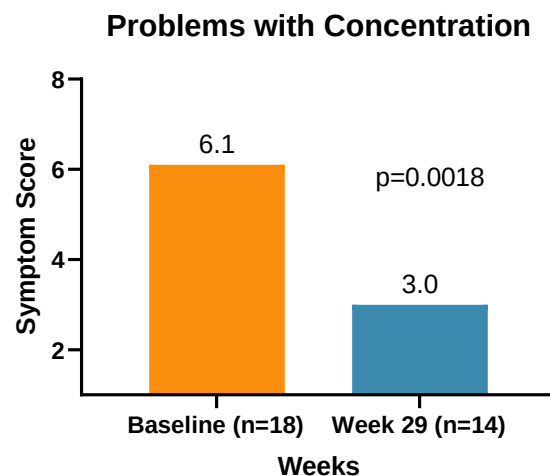
- Platelets increased post-baseline without significant clinical sequelae and stabilized over time

Data cutoff: 9 April 2024

Phase 2 REVIVE Study: Symptom Improvement

REVIVE Part 1: Improvement in PV related Symptoms

Symptom Improvements in Part 1 (28 Weeks)



Individual symptoms assessed using MPN-SAF; p-values are based on paired comparisons

Adapted from Kremyanskaya et al. EHA2023; Abstract LB2710.

REVIVE: Long-Term Safety Profile of Rusfertide

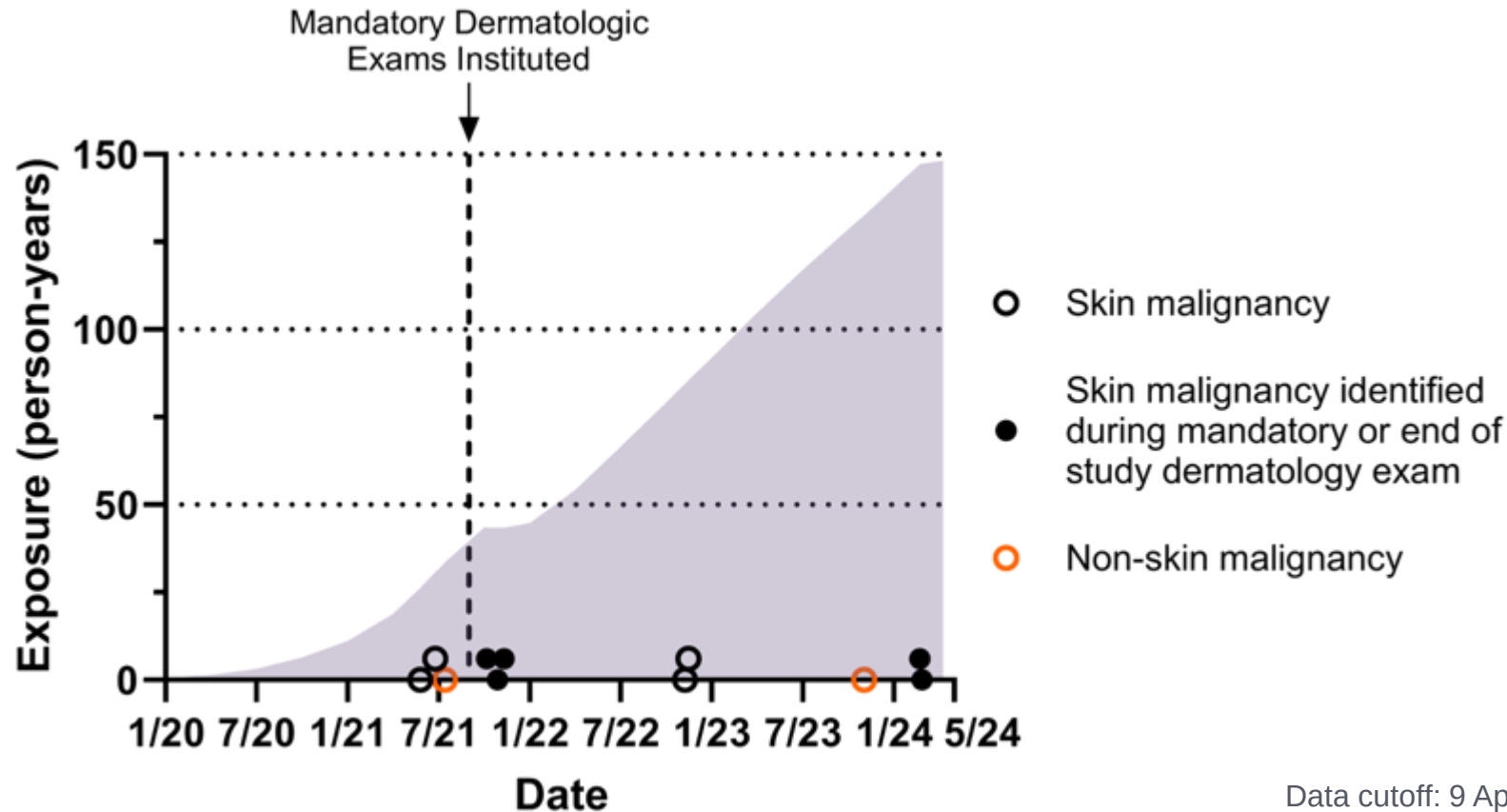
- The most common ($\geq 20\%$) TEAEs were injection site reactions, fatigue, COVID-19, pruritus, arthralgia, dizziness, nausea, anemia, and headache
 - Grade 3 TEAEs occurred in 25.7% of patients
 - There were no Grade 4 or 5 TEAEs
- No TEs occurred in low-risk patients
- 40 patients entered the study with high-risk PV
 - 14 patients had a TE prior to study entry
- 5 patients with high-risk PV developed 6 TEs on study
 - 2 of these patients had a TE prior to study entry
 - One patient with a portal vein thrombosis prior to study entry had an MI (Part 1; Week 10) and developed a recurrent MI (Part 3; Week 95); this patient remains ongoing on study (Week 108+)

Reported TEAEs (Any Grade) in ≥ 10 Patients	Overall, n (%)
Patients with at least 1 TEAE	70 (100.0)
Injection site erythema	46 (65.7)
Injection site pain	30 (42.9)
Injection site pruritus	27 (38.6)
Fatigue	25 (35.7)
COVID-19	22 (31.4)
Injection site mass	21 (30.0)
Pruritus	21 (30.0)
Arthralgia	19 (27.1)
Dizziness	19 (27.1)
Injection site swelling	17 (24.3)
Nausea	17 (24.3)
Anemia	16 (22.9)
Headache	16 (22.9)
Injection site irritation	14 (20.0)
Diarrhea	12 (17.1)
Injection site bruising	11 (15.7)
Dyspnea	10 (14.3)
Hyperhidrosis	10 (14.3)
Injection site warmth	10 (14.3)
Myalgia	10 (14.3)
Paresthesia	10 (14.3)
Upper respiratory tract infection	10 (14.3)

Adapted from Pettit, K. et al. Updated long-term results from the phase 2 REVIVE study investigating the hepcidin mimetic rusfertide in polycythemia vera patients: Hematocrit control and therapeutic phlebotomy frequency. EHA Library. 06/13/2024; 422322; S218.

Data cutoff: 9 April 2024

No Apparent Increase in Malignancies on Study With Increasing Exposure to Rusfertide



- 5 of 7 skin cancers were identified during mandatory dermatology exams that were implemented in September 2021

Rusfertide Summary

An Investigational Injectable Hepcidin Mimetic for Treatment of Polycythemia Vera

- PV patients requiring frequent phlebotomy $\pm$ cytoreductives have been treated with rusfertide for >3 years in the **REVIVE** study, with subjects remaining essentially phlebotomy free
 - Rapid, sustained and durable hematocrit control
 - Robust efficacy in all categories of patients including
 - Low and high risk patients
 - Patients on phlebotomy alone or on cytoreductives
 - Patients with high Hct (>48%)
 - Rusfertide dosing interruption leads to loss of effect; restart restores therapeutic benefits
 - Positive improvements in patient reported outcomes (PRO) symptom scores
 - Patients completing REVIVE have transitioned to additional 2-year open-label extension THRIVE study

- **REVIVE** study results published in NEJM¹

- Rapid Hct control (<45%) without phlebotomy in high Hct (>48%) **PACIFIC** study

- Rusfertide treatment with or without cytoreductives appears to be well tolerated

- Safety update presented at ASH in December 2023; no new safety signals observed²

- ~250 patient, randomized, placebo-controlled, global Ph3 **VERIFY** study to confirm efficacy and safety

- Enrollment completed in 1Q 2024
- 32-Week 1° EP completion and top-line results expected by end of Q1 2025

Clinical Study of Rusfertide in Patients with Hemochromatosis

Control Serum Iron and Reduce Phlebotomies

- Open-label, 24-week proof-of-concept study in patients with hereditary hemochromatosis
- Eligibility
 - Adults with HFE-related hemochromatosis.
 - History of ≥ 3 phlebotomies in 12 months or ≥ 4 phlebotomies in 15 months
- Clinical endpoints
 - Number of phlebotomies
 - Liver Iron Concentration (LIC) by MRI
- Manuscript published in *Lancet Gastroenterol Hepatol* in December 2023¹
 - Rusfertide treatment rapidly reduced and suppressed serum iron and TSAT
 - Essential elimination of phlebotomies and stable LIC
 - Rusfertide was generally well tolerated

